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Miu-chun [US/US]; 126 East Lincoln Avenue, Rahway, NJ
07065-0907 (US).

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(74) Common Representative: **MERCK & CO., INC.**; 126
East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

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(71) Applicant (*for all designated States except US*): **MERCK
& CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway,
NJ 07065-0907 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **WOOD, Michael, R.**
[US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-
0907 (US). **ANTHONY, Neville, J.** [GB/US]; 126 East
Lincoln Avenue, Rahway, NJ 07065-0907 (US). **BOCK,
Mark, G.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ
07065-0907 (US). **FENG, Dong-Mei** [US/US]; 126 East
Lincoln Avenue, Rahway, NJ 07065-0907 (US). **KUDUK,
Scott, D.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ
07065-0907 (US). **SU, Dai-Shi** [US/US]; 126 East Lin-
coln Avenue, Rahway, NJ 07065-0907 (US). **WAI, Jenny**

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(54) Title: N-BIPHENYLMETHYL AMINOCYCLOALKANECARBOXAMIDE DERIVATIVES WITH A SUBSTITUENT ON
THE METHYL USEFUL AS BRADYKININ ANTAGONISTS

(57) Abstract: N-Biphenyl(substituted methyl)aminocycloalkanecarboxamide derivatives are bradykinin B1 antagonists or inverse
agonists useful in the treatment or prevention of symptoms such as pain and inflammation associated with the bradykinin B1 pathway.

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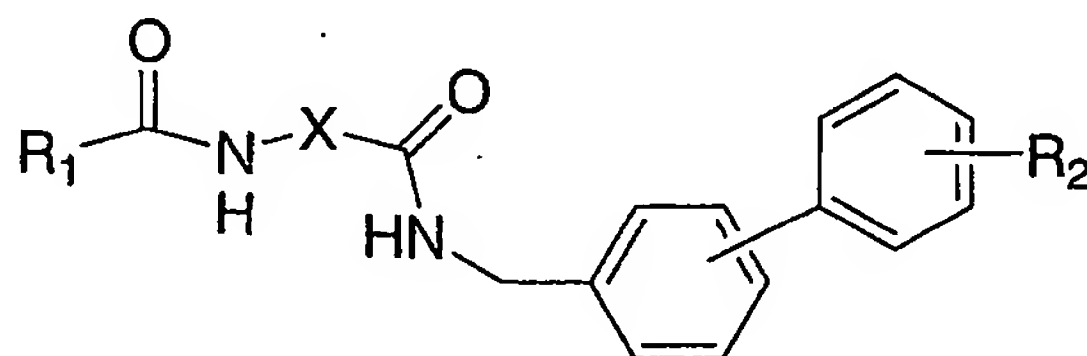
N-BIPHENYLMETHYL AMINOCYCLOALKANECARBOXAMIDE
DERIVATES WITH A SUBSTITUENT ON
THE METHYL USEFUL AS BRADYKININ ANTAGONISTS

5 BACKGROUND OF THE INVENTION

This invention is directed to aminocycloalkanecarboxamide compounds. In particular, this invention is directed to aminocycloalkanecarboxamide compounds that are bradykinin antagonists or inverse agonists.

Bradykinin ("BK") is a kinin which plays an important role in the
10 pathophysiological processes accompanying acute and chronic pain and inflammation. Bradykinin (BK), like other kinins, is an autacoid peptide produced by the catalytic action of kallikrein enzymes on plasma and tissue precursors termed kininogens. The biological actions of BK are mediated by at least two major G-protein-coupled BK receptors termed B1 and B2. It is generally believed that B2 receptors, but not B1
15 receptors, are expressed in normal tissues and that inflammation, tissue damage or bacterial infection can rapidly induce B1 receptor expression. This makes the B1 receptor a particularly attractive drug target. The putative role of kinins, and specifically BK, in the management of pain and inflammation has provided the impetus for developing potent and selective BK antagonists. In recent years, this
20 effort has been heightened with the expectation that useful therapeutic agents with analgesic and anti-inflammatory properties would provide relief from maladies mediated through a BK receptor pathway (see e.g., M.G. Bock and J. Longmore, *Current Opinion in Chem. Biol.*, 4:401-406(2000)). Accordingly, there is a need for novel compounds that are effective in blocking or reversing activation of bradykinin
25 receptors. Such compounds would be useful in the management of pain and inflammation, as well as in the treatment or prevention of diseases and disorders mediated by bradykinin; further, such compounds are also useful as research tools (*in vivo* and *in vitro*).

Canadian Published Application No. 2,050,769 discloses compounds
30 of the formula:



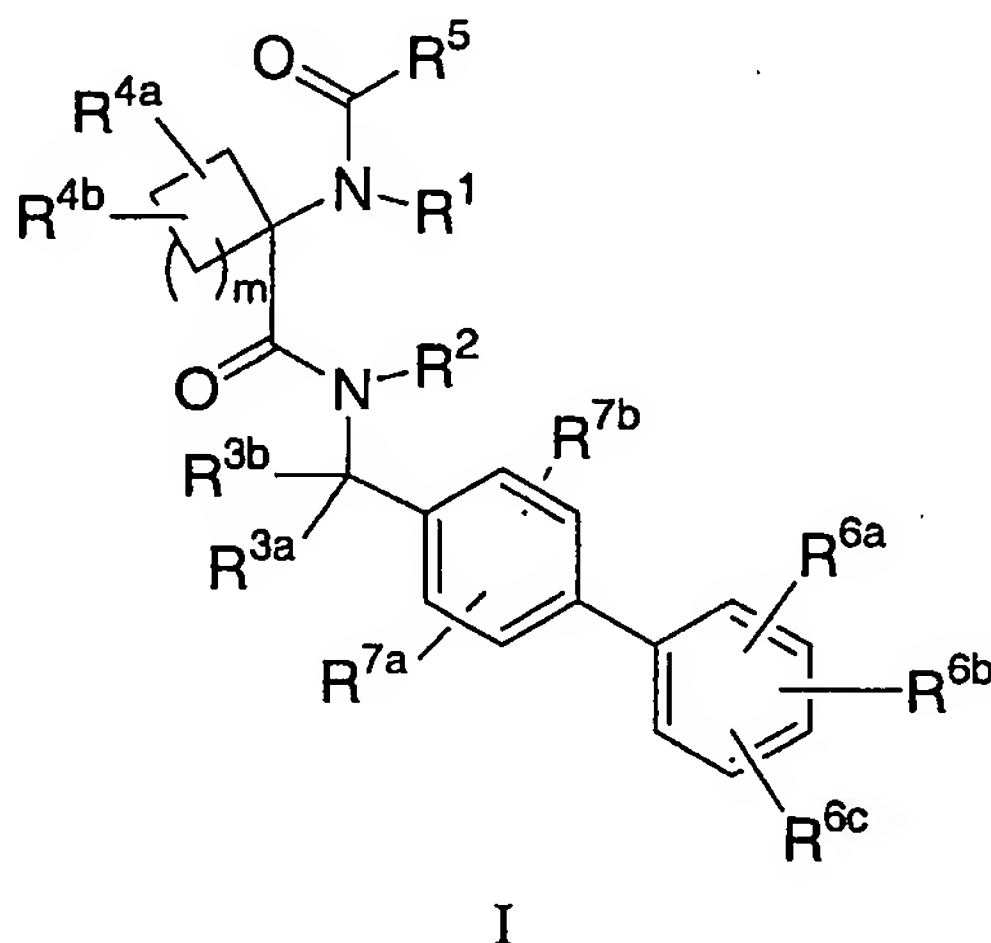
which are intermediates in the preparation of angiotensin II antagonists.

SUMMARY OF THE INVENTION

The present invention provides biphenyl cycloalkanecarboxamide derivatives which are bradykinin antagonists or inverse agonists, pharmaceutical compositions containing such compounds, and methods of using them as therapeutic agents.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds of formula I and pharmaceutically acceptable salts thereof:



wherein

R¹ and R² are independently selected from

- (1) hydrogen and
- (2) C₁₋₄ alkyl;

R^{3a} is selected from

- (1) hydrogen and
- (2) C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms;

R^{3b} is C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms;

R^{4a} and R^{4b} are independently selected from

- (1) hydrogen,
- (2) halogen, and

- (3) C₁₋₄ alkyl optionally substituted with 1 to 4 groups selected from halogen, OR^a, OC(O)R^a, S(O)_kR^d, OS(O)₂R^d, and NR¹R², or R^{4a} and R^{4b} together with the carbon atom to which they are both attached form an exo-cyclic methylene optionally substituted with 1 to 2 groups selected from C₁₋₄ alkyl optionally substituted with 1-5 halogens and C₁₋₄ alkyloxy;
 5 R⁵ is selected from
- (1) C₁₋₆ alkyl optionally substituted with 1 to 5 groups independently selected from halogen, nitro, cyano, OR^a, SR^a, COR^a, SO₂R^d, CO₂R^a, OC(O)R^a, NR^bR^c, NR^bC(O)R^a, NR^bC(O)₂R^a, C(O)NR^bR^c, C₃₋₈ cycloalkyl,
 10 (2) C₃₋₈ cycloalkyl optionally substituted with 1 to 5 groups independently selected from halogen, nitro, cyano and phenyl,
- (3) C₃₋₆ alkynyl,
 (4) C₂₋₆ alkenyl optionally substituted with hydroxyethyl,
 15 (5) (CH₂)_k-aryl optionally substituted with 1 to 3 groups independently selected from halogen, nitro, cyano, OR^a, SR^a, C(O)₂R^a, C₁₋₄ alkyl and C₁₋₃ haloalkyl, wherein aryl is selected from phenyl, 3,4-methylenedioxyphenyl and naphthyl;
- (6) (CH₂)_k-heterocycle optionally substituted with 1 to 3 groups
 20 independently selected from halogen, nitro, cyano, OR^a, SR^a, C₁₋₄ alkyl and C₁₋₃ haloalkyl wherein said heterocycle is selected from (a) a 5-membered heteroaromatic ring having a ring heteroatom selected from N, O and S, and optionally having up to 3 additional ring nitrogen atoms wherein said ring is optionally benzo-fused; (b) a 6-membered heteroaromatic ring containing from 1 to 3 ring nitrogen atoms and N-oxides thereof, wherein said ring is optionally benzo-fused; and (c) a 5- or 6-membered non-aromatic heterocyclic ring selected from tetrahydrofuranyl, 5-oxo-tetrahydrofuranyl, 2-oxo-2H-pyranyl, 6-oxo-1,6-dihydropyridazinyl,
 25 (7) C(O)₂R^a, and
 (8) C(O)NR^bR^c;
- 30 R^{6a} is selected from
- (1) C₁₋₈ alkyl optionally substituted with 1-5 groups independently selected from halogen, nitro, cyano, COR^a, CO₂R^a, C(O)NR^bR^c, OR^a, OC(O)R^a, SR^a, SO₂R^d, S(O)R^d, NR^bR^c, NR^bC(O)R^a, NR^bSO₂R^d, NR^bCO₂R^a,
 (2) C₃₋₈ cycloalkyl,

- 5 (3) C₂₋₈ alkenyl optionally substituted with CO₂R^a,
 (4) halogen,
 (5) cyano,
 (6) nitro,
 (7) NR^bR^c,
 (8) NR^bC(O)R^a,
 (9) NR^bCO₂R^a,
 (10) NR^bC(O)NR^bR^c,
 (11) NR^bC(O)NR^bCO₂R^a,
 10 (12) NR^bSO₂R^d,
 (13) CO₂R^a,
 (14) COR^a,
 (15) C(O)NR^bR^c,
 (16) C(O)NHO R^a,
 15 (17) C(=NOR^a)R^a,
 (18) C(=NOR^a)NR^bR^c,
 (19) OR^a,
 (20) OC(O)R^a,
 (21) S(O)_kR^d,
 20 (22) SO₂NR^bR^c, and
 (23) optionally substituted heterocycle where the heterocycle is a 5-
 membered heteroaromatic ring having a ring heteroatom selected from N, O and S,
 and optionally having up to 3 additional ring nitrogen atoms, 4,5-dihydro-oxazolyl
 and 4,5-dihydro-1,2,4-oxadiazolyl, and wherein said substituent is 1 to 3 groups
 25 independently selected from C₁₋₄ alkyl optionally substituted with 1 to 5 halogen
 atoms, OR^a or OC(O)R^a,
 R^{6b} and R^{6c} are independently selected from
 (1) hydrogen, and
 (2) a group from R^{6a}; with the proviso that not more than one of
 30 R^{6a}, R^{6b}, and R^{6c} is a heterocycle;
 R^{7a} and R^{7b} are independently selected from
 (1) hydrogen,
 (2) halogen,
 (3) cyano,

- 5
- (4) nitro,
 - (5) OR^a,
 - (6) CO₂R^a,
 - (7) C(O)NR^bR^c,
 - (8) C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms,
 - (9) NR^bR^c, and
 - (10) S(O)_kR^d;

R^a is selected from

- 10
- (1) hydrogen,
 - (2) C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms,
 - (3) phenyl optionally substituted with 1 to 3 groups independently selected from halogen, cyano, nitro, OH, C₁₋₄ alkyloxy, C₃₋₆ cycloalkyl and C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms,
 - (4) C₃₋₆ cycloalkyl, and
 - 15 (5) pyridyl optionally substituted with 1 to 3 groups independently selected from halogen and C₁₋₄ alkyl;

R^b and R^c are independently selected from

- (1) hydrogen,
- (2) C₁₋₄ alkyl optionally substituted with 1 to 5 groups
- 20 independently selected from halogen, amino, mono-C₁₋₄alkylamino, di-C₁₋₄alkylamino, and SO₂R^d,
- (3) (CH₂)_k-phenyl optionally substituted with 1 to 3 groups selected from halogen, cyano, nitro, OH, C₁₋₄ alkyloxy, C₃₋₆ cycloalkyl and C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms, and
- 25 (4) C₃₋₆ cycloalkyl, or

R^b and R^c together with the nitrogen atom to which they are attached form a 4-, 5-, or 6-membered ring optionally containing an additional heteroatom selected from N, O, and S; or

30 R^b and R^c together with the nitrogen atom to which they are attached form a cyclic imide;

R^d is selected from

- (1) C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms,
- (2) C₁₋₄ alkyloxy, and

(3) phenyl optionally substituted with 1 to 3 groups selected from halogen, cyano, nitro, OH, C₁₋₄ alkyloxy, C₃₋₆ cycloalkyl and C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms;

k is 0, 1 or 2; and

5 m is 0 or 1.

For compounds of formula I, examples of R¹ and R² include hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl and sec-butyl. In one embodiment of formula I are compounds wherein R¹ and R² are each hydrogen.

10 Examples of R^{3a} and R^{3b} for compounds of formula I include hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, chloromethyl, fluromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 1,1,2,2,2-pentafluoroethyl, and the like. In one embodiment of formula I are compounds wherein one of R^{3a} is hydrogen and R^{3b} is C₁₋₄ alkyl. In one subset
15 thereof R^{3b} is methyl.

Examples R^{4a} and R^{4b} for compounds of formula I include hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, t-butyl, chlorine, fluorine, bromine, chloromethyl, 1-chloroethyl, hydroxymethyl, 2-methoxyethyl, ethoxymethyl, acetyloxymethyl, methylthiomethyl, aminomethyl, methylamino-
20 methyl, (dimethylamino)methyl, (methylsulfonyl)oxymethyl, and the like; or R^{4a} and R^{4b} on the same carbon atom taken together represent methylene. In one embodiment of formula I are compounds wherein one of R^{4a} and R^{4b} is hydrogen and the other is selected from hydrogen, halogen and C₁₋₄ alkyl optionally substituted with a group selected from halogen, OR^a, OC(O)R^a, S(O)_kR^d, OS(O)₂R^d, and
25 NR¹R², or R^{4a} and R^{4b} together with the carbon atom to which they are both attached form an exo-cyclic methylene. In one subset thereof R^{4a} and R^{4b} are each hydrogen; in another subset R^{4a} is hydrogen and R^{4b} is selected from CH₂-halogen, CH₂-OR^a, CH₂-OC(O)R^a, CH₂-S(O)_kR^d, CH₂-OS(O)₂R^d, and CH₂-NR¹R²; in a further subset R^{4a} is hydrogen and R^{4b} is selected from hydroxymethyl,
30 acetyloxymethyl, chloromethyl, (methanesulfonyl)oxymethyl, (methylthio)methyl and (dimethylamino)methyl.

Examples of R⁵ for compounds of formula I include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, t-butyl, 1-ethylpropyl, 2,2-dimethylpropyl, bromomethyl, chloromethyl, dichloromethyl, difluoromethyl, trifluoromethyl, chlorodifluoromethyl, cyanomethyl, aminomethyl, acetylaminomethyl, dimethyl-

aminomethyl, hydroxymethyl, methoxymethyl, ethoxymethyl, methylsulfonylmethyl, phenylthiomethyl, phenoxymethyl, 1-aminoethyl, 1-acetylaminomethyl, 1-imidazolylmethyl, t-butoxycarbonylaminomethyl, 3-pyridylcarbonylmethyl, 1-chloroethyl, 1,1-dichloroethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 2-methoxyethyl, 2-phenylethyl, 2-cyclopentylethyl, 2-carboxyethyl, 2-methoxy-2-oxoethyl, 2-nitroethyl, 1,1-difluoro-1-hydroxypropyl, 1-hydroxypropyl, 2-oxopropyl, 3-methoxy-3-oxopropyl, 1-cyanocyclopropyl, cyclopropyl, cyclopentyl, 2-phenylcyclopropyl, allyl, ethenyl, 1-(1-hydroxyethyl)vinyl, 3-butynyl, propargyl, phenyl, benzyl, 3,5-bis(trifluoromethyl)phenyl, 2,4-difluorophenyl, 4-methylphenyl, 3,4-dimethoxybenzyl, 3,4-dimethoxyphenyl, 4-cyanophenyl, 3-nitrophenyl, 2-naphthyl, 3,4-methylenedioxyphenyl, 3-cyanophenyl, 2-cyanophenyl, 3-fluorophenyl, 3-methoxyphenyl, 3-chlorophenyl, 3,4-dichlorophenyl, 3,5-dimethoxyphenyl, 3-trifluoromethylphenyl, 3-methylphenyl, 3,5-dichlorophenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 3-nitro-5-(trifluoromethyl)phenyl, 5-isoxazolyl, 2-benzothienyl, 2-thienylmethyl, 3-pyridyl, 4-pyridyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 5-methyl-3-isoxazolyl, 3-tetrahydrofuranyl, 4-methyl-1,2,5-oxadiazol-3-yl, 5-carboxy-3-pyridyl, 6-hydroxy-2-pyridyl, 5-hydroxy-3-pyridyl, 2-hydroxy-3-pyridyl, 2-methoxy-3-pyridyl, 6-chloro-2-pyridyl, 2-chloro-3-pyridyl, 5-chloro-3-pyridyl, 5-fluoro-3-pyridyl, 5-bromo-3-pyridyl, 5-methyl-3-pyridyl, 3-(trifluoromethyl)-4-pyridyl, 5-(trifluoromethyl)-3-pyridyl, 1-methyl-4-pyrazolyl, 1-pyrazolylmethyl, 1-methyl-2-imidazolyl, 1,2,4-triazol-1-ylmethyl, 4-thiazolyl, 5-oxotetrahydrofuran-2-yl, 2-oxo-5-pyranyl, 3-isoxazolyl, 3-pyridazinyl, 5-pyrimidinyl, 4-pyrimidinyl, 1-methyl-5-pyrazolyl, 1-methyl-3-pyrazolyl, 5-thiazolyl, 5-methyl-1-pyrazolylmethyl, (3-methyl-1,2,4-triazol-5-yl)methyl, 2-(1,2,4-triazol-1-yl)ethyl, 5-methyl-4-thiazolyl, 2-quinoxaliny, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, 2-(dimethylamino)ethylaminocarbonyl, benzylaminocarbonyl, 2-phenethylaminocarbonyl.

In one embodiment of formula I are compounds wherein R⁵ is C₁₋₆ alkyl optionally substituted with 1 to 5 groups independently selected from halogen, nitro, cyano, OR^a, SR^a, COR^a, SO₂R^d, CO₂R^a, OC(O)R^a, NR^bR^c, NR^bC(O)R^a, NR^bCO₂R^a, C(O)NR^bR^c, and C₃₋₈ cycloalkyl. In one subset thereof are compounds wherein R⁵ is C₁₋₅ alkyl optionally substituted with 1 to 5 groups independently selected from halogen, nitro, cyano, OR^a, SR^a, CO₂R^a and C₃₋₈ cycloalkyl. In a further subset are compounds wherein R⁵ is selected from C₁₋₅ alkyl and C₁₋₃ alkyl substituted with 1 to 5 groups selected from halogen, cyano, hydroxy, C₁₋₄ alkoxy and C₁₋₄ alkoxycarbonyl. In another further subset R⁵ is selected from C₁₋₃ alkyl

substituted with 1 to 5 halogen atoms, or a group selected from cyano, hydroxy, C₁₋₄ alkoxy and C₁₋₄ alkoxycarbonyl.

In another embodiment of formula I are compounds wherein R⁵ is C₃₋₆ cycloalkyl optionally substituted with 1 to 3 groups independently selected from halogen, nitro, cyano and phenyl. In one subset R⁵ is C₃₋₆ cycloalkyl optionally substituted with a group selected from cyano and phenyl.

In another embodiment of formula I are compounds wherein R⁵ is (CH₂)_k-aryl optionally substituted with 1 to 3 groups independently selected from halogen, nitro, cyano, OR^a, SR^a, C₁₋₄ alkyl and C₁₋₃ haloalkyl, wherein aryl is selected from phenyl, 3,4-methylenedioxyphenyl and naphthyl. In one subset thereof, R⁵ is phenyl optionally substituted with 1 to 3 groups independently selected from halogen, trifluoromethyl, nitro, cyano, C₁₋₄ alkoxy and C₁₋₄ alkyl; in a further subset R⁵ is phenyl optionally substituted with 1 to 2 groups selected from methyl, trifluoromethyl, halogen, cyano, nitro and methoxy.

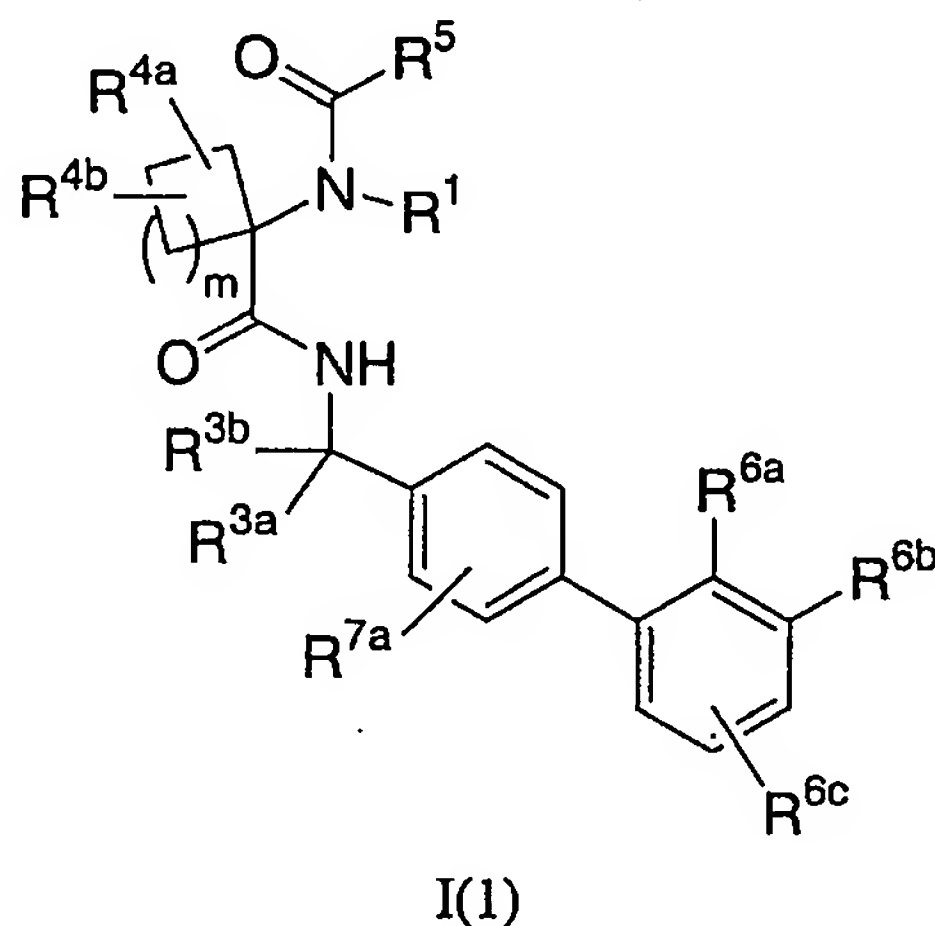
In another embodiment of formula I are compounds wherein R⁵ is (CH₂)_k-heterocycle optionally substituted with 1 to 2 groups independently selected from halogen, nitro, cyano, OR^a, SR^a, C₁₋₄ alkyl and C₁₋₃ haloalkyl wherein said heterocycle is selected from isoxazolyl, thienyl, pyridinyl, benzothienyl, furyl, tetrahydrofuranyl, oxadiazolyl, 1-oxidopyridinyl, pyrazolyl, imidazolyl, 1,2,4-triazolyl, thiazolyl, 5-oxotetrahydrofuranyl, 2-oxo-2H-pyranyl, 6-oxo-1,6-dihydropyridazinyl, oxazolyl, pyridazinyl, pyrimidinyl and quinoxalinyl. In one subset thereof R⁵ is selected from isoxazolyl optionally substituted with 1 or 2 C₁₋₄ alkyl, thienyl, pyridinyl optionally substituted with hydroxy, trifluoromethyl or halogen, benzothienyl, furyl, tetrahydrofuranyl, oxadiazolyl optionally substituted with C₁₋₄ alkyl, 1-oxidopyridinyl optionally substituted with halogen or C₁₋₄ alkyl, pyrazolyl optionally substituted with C₁₋₄ alkyl, imidazolyl optionally substituted with C₁₋₄ alkyl, 1,2,4-triazolyl optionally substituted with C₁₋₄ alkyl, thiazolyl optionally substituted with C₁₋₄ alkyl, 5-oxotetrahydrofuranyl, 2-oxo-2H-pyranyl, 6-oxo-1,6-dihydropyridazinyl, oxazolyl, pyridazinyl, pyrimidinyl and quinoxalinyl. In another subset R⁵ is selected from 5-isoxazolyl, 5-pyrimidinyl, 5-bromo-3-pyridyl and N-oxide thereof, and 5-trifluoromethyl-3-pyridyl.

For compounds of formula I examples of R^{6a} include 1-methylethyl, 1-hydroxyethyl, methoxymethyl, 2-oxo-2-methoxyethyl, carboxy, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, phenoxycarbonyl, cyclopentoxycarbonyl, cyclo-

butoxycarbonyl, cyclopropoxycarbonyl, 2,2,2-trifluoroethoxycarbonyl, 4-trifluoromethylphenoxycarbonyl, methoxyaminocarbonyl, methoxycarbonylmethyl, formyl, hydroxy, 3-methyl-1,2,4-oxadiazol-5-yl, 5-methyl-1,2,4-oxadiazol-3-yl, 1-methyl-5-tetrazolyl, 2-methyl-5-tetrazolyl, cyano, hydroxy, methoxy, difluoromethoxy, trifluoromethoxy, trifluoromethyl, chloro, fluoro, methylaminosulfonyl, dimethylaminosulfonyl, methoxycarbonylamino, ethoxycarbonylamino, 2-fluoroethoxycarbonylamino, isopropoxycarbonylamino, methylaminocarbonylamino, dimethylamino, methylaminocarbonyl, isopropylaminocarbonyl, ethylaminocarbonyl, cyclopropylaminocarbonyl, cyclobutylaminocarbonyl, dimethylaminocarbonyl and aminocarbonyl; examples for R^{6b} for compounds of formula I include hydrogen, chloro, fluoro, methyl and methoxycarbonyl; example of R^{6c} include hydrogen, chloro, fluoro and methyl; and examples of R^{7a} and R^{7b} include hydrogen, hydroxy, methoxy, methylamino, methylsulfonyl, chloro and fluoro.

In another embodiment of formula I are compounds wherein m is 0.

In another embodiment of formula I are compounds represented by formula I(1):



wherein m , R^1 , R^2 , R^{3a} , R^{3b} , R^{4a} , R^{4b} , R^5 , R^{6a} , R^{6b} , R^{6c} and R^{7a} have the same definitions as provided under formula I.

In a subset of formula I(1) are compounds wherein R^{6a} is selected from (1) CO_2R^a , (2) $C(O)NHR^a$, (3) cyano, (4) halogen, (5) OR^a , (6) C_{1-8} alkyl optionally substituted with 1-5 halogen atoms, or a group selected from CO_2R^a , $C(O)NR^bR^c$ and OR^a , (7) $C(O)NR^bR^c$, (8) $NR^bC(O)NR^bR^c$, (9) $NR^bC(O)OR^a$, and (10) optionally substituted heterocycle where the heterocycle is selected from

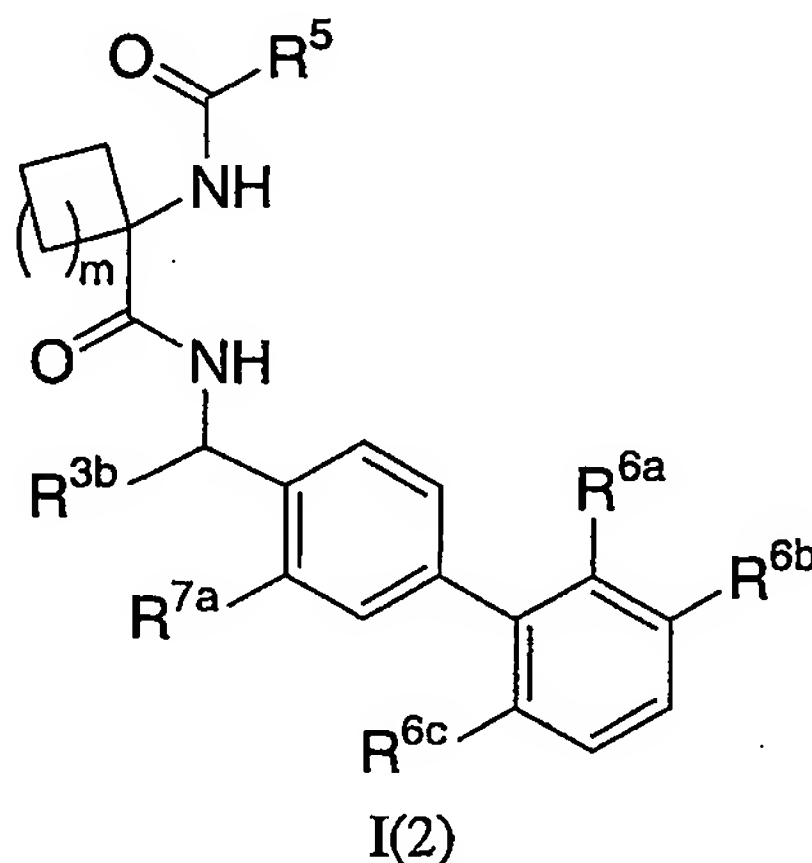
oxadiazolyl and tetrazolyl and wherein said substituent is 1 to 3 groups independently selected from C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms, OR^a or OC(O)R^a. In a further subset are compounds wherein R^{6a} is selected from CO₂R^a, C(O)NHOR^a, methyltetrazolyl, methyloxadiazolyl, NR^bC(O)NR^bR^c, and
 5 NR^bC(O)OR^a.

In another subset of formula I(1) are compounds wherein R^{6b} is selected from hydrogen, halogen and CO₂R^a. In a further subset R^{6b} is hydrogen or halogen.

In another subset of formula I(1) are compounds where R^{6a} is selected
 10 from (1) CO₂R^a, (2) C(O)NHOR^a, (3) cyano, (4) halogen, (5) OR^a, (6) C₁₋₈ alkyl optionally substituted with 1-5 halogen atoms, or a group selected from CO₂R^a, C(O)NR^bR^c and OR^a, (7) C(O)NR^bR^c, (8) NR^bC(O)NR^bR^c, (9) NR^bC(O)OR^a, and (10) optionally substituted heterocycle where the heterocycle is selected from
 15 oxadiazolyl and tetrazolyl and wherein said substituent is 1 to 3 groups independently selected from C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms, OR^a or OC(O)R^a; R^{6b} is selected from hydrogen and halogen; and R^{6c} is hydrogen.

In another subset of formula I(1) are compounds wherein R⁵ is selected from C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms or a cyano group, C₃₋₆ cycloalkyl, isoxazolyl, pyrimidinyl and pyridinyl (and N-oxide thereof)
 20 optionally substituted with halogen.

In another embodiment of formula I are compounds represented by formula I(2):



25

wherein m, R^{3b}, R⁵, R^{6a}, R^{6b}, R^{6c} and R^{7a} have the same definitions as provided under formula I.

In one embodiment of formula I(2), R^{3b} is methyl.

In another embodiment of formula I(2), R^{6b} is hydrogen or halogen.

In one subset R^{6b} is hydrogen; in another subset R^{6b} is fluorine or chlorine.

In another embodiment of formula I(2), R^{6a} is selected from (1) CO₂R^a, (2) C(O)NHOR^a, (3) cyano, (4) halogen, (5) OR^a, (6) C₁₋₈ alkyl optionally substituted with 1-5 halogen atoms, or a group selected from CO₂R^a, C(O)NR^bR^c and OR^a, (7) C(O)NR^bR^c, (8) NR^bC(O)NR^bR^c, (9) NR^bC(O)OR^a, and (10) optionally substituted heterocycle where the heterocycle is selected from oxadiazolyl and tetrazolyl and wherein said substituent is 1 to 3 groups independently selected from C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms, OR^a or OC(O)R^a. In one subset R^{6a} is selected from CO₂R^a, C(O)NHOR^a, methyltetrazolyl, methyloxadiazolyl, NR^bC(O)NR^bR^c, and NR^bC(O)OR^a. In a further subset R^{6a} is selected from CO₂R^a, methyltetrazolyl and methyloxadiazolyl,

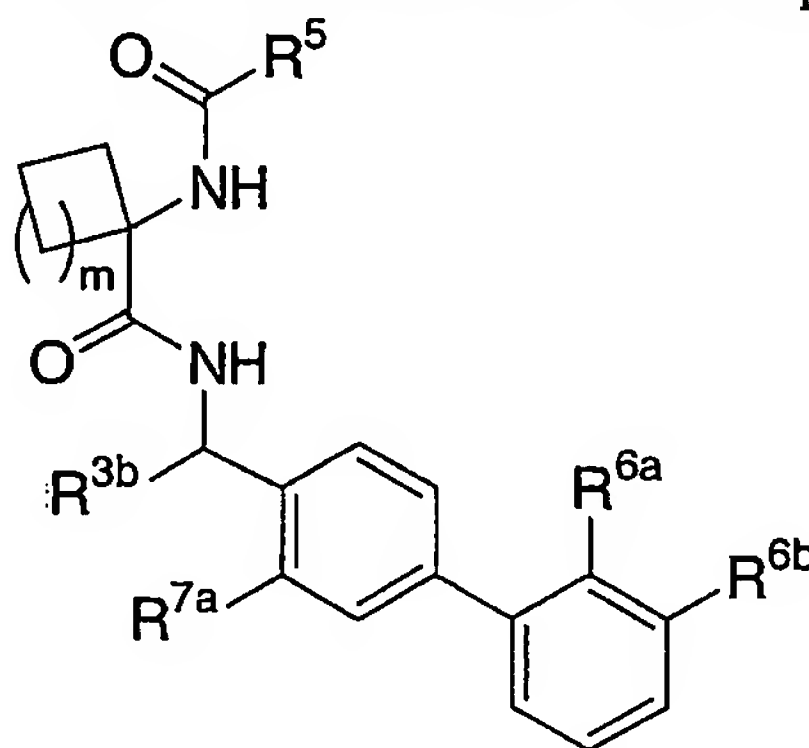
In another embodiment of formula I(2), R^{6c} is hydrogen or halogen.

In one subset R^{6c} is hydrogen.

In another embodiment R^{7a} is hydrogen or halogen. In one subset R^{7a} is hydrogen. In another subset R^{7a} is fluorine. In yet another subset R^{6b} is hydrogen, fluorine or chlorine, and R^{7a} is hydrogen or fluorine.

In another embodiment of formula I(2) R⁵ is selected from C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms or a cyano group, C₃₋₆ cycloalkyl, isoxazolyl, pyrimidinyl and pyridinyl (and N-oxide thereof) optionally substituted with halogen.

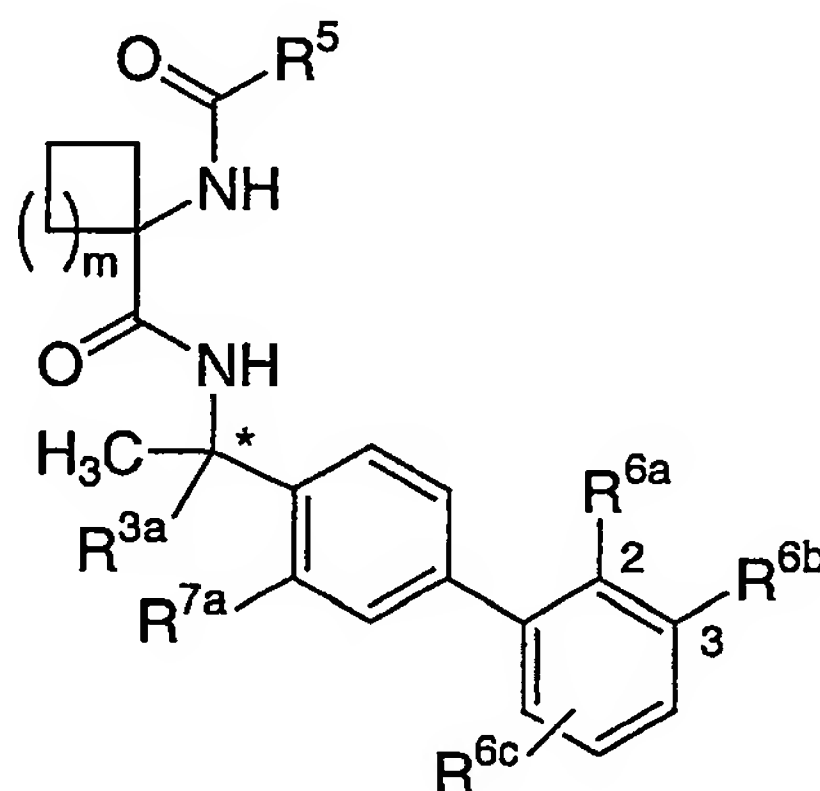
In another embodiment of formula I are compounds of formula I(3):



I(3)

wherein m is 0 or 1, R^{6a} is 2-methyl-2H-tetrazol-5-yl, 3-methyl-1,2,4-oxadiazol-5-yl, CO₂R^a or C(O)NHO R^a wherein R^a is C₁₋₄ alkyl, particularly methyl; R^{6b} is hydrogen, fluorine or chlorine; R^{3b} is C₁₋₄ alkyl, particularly methyl; R⁵ is selected from C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms or a cyano group, C₃₋₆ cycloalkyl, isoxazolyl, pyrimidinyl and pyridinyl (and N-oxide thereof) optionally substituted with halogen or trifluoromethyl, particularly trifluoromethyl, difluoromethyl, chlorodifluoromethyl, 2,2,2-trifluoroethyl, pentafluoromethyl, cyanomethyl, 5-pyrimidinyl, 5-isoxazolyl and 5-bromo-3-pyridinyl and N-oxide thereof; and R^{7a} is hydrogen or fluorine.

10 Some representative compounds are:



m	R5	R6a	R6b	R6c	R7a	*
R3a is H unless otherwise specified						
0	CH ₂ CF ₃	CO ₂ CH ₃	F	H	H	R
0	CH ₂ CF ₃	CONHOCH ₃	F	H	H	R
0	CF ₃	CO ₂ CH ₃	F	H	H	§
0	CF ₃	3-CH ₃ -1,2,4-oxadiazol-5-yl	F	H	F	R
0	CF ₃	CO ₂ CH ₃	Cl	H	F	R
0	CF ₃	2-CH ₃ -tetrazol-5-yl	F	H	F	R
0	CH ₂ CN	CO ₂ CH ₃	F	H	H	R
0	CH ₂ CN	CO ₂ CH ₃	Cl	H	H	R
0	CH ₂ CF ₃	CO ₂ CH ₃	Cl	H	H	R
0	CH ₂ CF ₃	CO ₂ CH ₃	F	H	F	(±)
0	isoxazol-5-yl	CO ₂ CH ₃	F	H	F	(±)

m	R5	R6a	R6b	R6c	R7a	*
0	CH ₂ CN	CO ₂ CH ₃	F	H	F	(±)
0	pyrimidin-5-yl	CO ₂ CH ₃	F	H	H	R
0	CH ₂ CF ₃	CO ₂ CH ₃	F	H	F	S
0	CH ₂ CF ₃	CO ₂ CH ₃	F	H	F	R
0	pyrimidin-5-yl	CO ₂ CH ₃	F	H	F	(±)
0	isoxazol-5-yl	CO ₂ CH ₃	F	H	F	R
0	CF ₃	CO ₂ CH ₃	F	H	F	R
0	pyrimidin-5-yl	CO ₂ CH ₃	F	H	F	R
0	isoxazol-5-yl	CO ₂ CH ₃	F	H	F	S
0	CF ₃	CO ₂ CH ₃	F	H	F	S
0	pyrimidin-5-yl	CO ₂ CH ₃	F	H	F	S
0	CH ₃	CO ₂ CH ₃	F	H	F	R
0	5-Br-pyridin-3-yl	CO ₂ CH ₃	F	H	F	R
0	5-Br-1-oxido-pyridin-3-yl	CO ₂ CH ₃	F	H	F	R
0	CF ₃	CO ₂ CH ₃	H	H	F	R
0	pyrimidin-5-yl	CO ₂ CH ₃	H	H	F	R
0	CClF ₂	CO ₂ CH ₃	F	H	F	R
0	5-(CF ₃)pyridin-3-yl	CO ₂ CH ₃	F	H	F	R
0	CClF ₂	CO ₂ CH ₃	Cl	H	F	R
0	CHF ₂	CO ₂ CH ₃	F	H	F	R
0	CF ₂ CF ₃	CO ₂ CH ₃	F	H	F	R
0	CHF ₂	CO ₂ CH ₃	Cl	H	F	R
0	CH ₃	3-CH ₃ -1,2,4-oxadiazol-5-yl	F	H	H	R
0	CH ₂ CN	3-CH ₃ -1,2,4-oxadiazol-5-yl	F	H	H	R
0	CH ₂ CF ₃	3-CH ₃ -1,2,4-oxadiazol-5-yl	F	H	H	R
0	isoxazol-5-yl	3-CH ₃ -1,2,4-oxadiazol-5-yl	F	H	H	R
0	CH ₂ CF ₃	3-CH ₃ -1,2,4-oxadiazol-5-yl	F	H	F	S
0	CH ₂ CF ₃	3-CH ₃ -1,2,4-oxadiazol-5-yl	F	H	F	R
0	CH ₂ CN	3-CH ₃ -1,2,4-oxadiazol-5-yl	F	H	F	(±)

m	R5	R6a	R6b	R6c	R7a	*
0	CH ₂ CF ₃	3-CH ₃ -1,2,4-oxadiazol-5-yl	F	H	F	(±)
0	pyrimidin-5-yl	3-CH ₃ -1,2,4-oxadiazol-5-yl	F	H	F	(±)
0	CClF ₂	3-CH ₃ -1,2,4-oxadiazol-5-yl	F	H	F	R
0	pyrimidin-5-yl	3-CH ₃ -1,2,4-oxadiazol-5-yl	F	H	F	R
0	CHF ₂	3-CH ₃ -1,2,4-oxadiazol-5-yl	F	H	F	R
0	CH ₂ CN	2-CH ₃ -tetrazol-5-yl	F	H	H	R
0	CH ₂ CF ₃	2-CH ₃ -tetrazol-5-yl	F	H	H	R
0	CH ₂ CN	1-CH ₃ -tetrazol-5-yl	F	H	H	R
0	CH ₂ CF ₃	1-CH ₃ -tetrazol-5-yl	F	H	H	R
0	CH ₃	1-CH ₃ -tetrazol-5-yl	F	H	H	R
0	isoxazol-5-yl	2-CH ₃ -tetrazol-5-yl	F	H	F	(±)
0	CH ₂ CF ₃	2-CH ₃ -tetrazol-5-yl	F	H	F	(±)
0	pyrimidin-5-yl	2-CH ₃ -tetrazol-5-yl	F	H	F	(±)
0	CF ₃	2-CH ₃ -tetrazol-5-yl	F	H	F	S
0	CClF ₂	2-CH ₃ -tetrazol-5-yl	F	H	F	R
0	CHF ₂	2-CH ₃ -tetrazol-5-yl	F	H	F	R
0	CH ₂ CF ₃	cyano	F	H	H	R
0	CH ₂ CF ₃	difluoromethoxy	H	H	H	R
0	CH ₂ CF ₃	trifluoromethoxy	H	H	H	R
0	CH ₂ CF ₃	trifluoromethyl	F	H	H	R
0	CH ₂ CF ₃	Cl	Cl	H	H	R
0	isoxazol-5-yl	trifluoromethyl	F	H	H	R
0	CH ₂ CN	trifluoromethyl	F	H	H	R
0	isoxazol-5-yl	Cl	Cl	H	H	R
0	CH ₂ CN	Cl	Cl	H	H	R
0	CH ₂ CN	F	CO ₂ Me	H	H	R
0	cyclopropyl	cyano	F	H	H	R
0	CH ₂ CF ₃	CON(CH ₃) ₂	F	H	H	R
0	pyrimidin-5-yl	NHCO ₂ CH ₃	F	H	H	R
0	pyrimidin-5-yl	NHCONHCH ₃	F	H	H	R
0	CF ₃	CONHCH ₃	F	H	H	R
0	CF ₃	CONHCH ₃	Cl	H	H	R

m	R ⁵	R ^{6a}	R ^{6b}	R ^{6c}	R ^{7a}	*
0	CH ₂ CF ₃	CONHCH ₃	F	H	H	R
0	isoxazol-5-yl	CONHOCH ₃	F	H	H	R
0	CH ₂ CF ₃	CONH-cyclopropyl	F	H	H	R
0	CH ₂ CF ₃	CONH-cyclobutyl	F	H	H	R
0	CH ₂ CF ₃	5-CH ₃ -1,2,4-oxadiazol-3-yl	F	H	H	R
0	isoxazol-5-yl	5-CH ₃ -1,2,4-oxadiazol-3-yl	F	H	H	R
0	pyrimidin-5-yl	5-CH ₃ -1,2,4-oxadiazol-3-yl	H	H	F	R
0	CF ₃	5-CH ₃ -1,2,4-oxadiazol-3-yl	H	H	F	R
0	pyrimidin-5-yl	5-CH ₃ -1,2,4-oxadiazol-3-yl	H	5-Cl	F	R
0	CF ₃	5-CH ₃ -1,2,4-oxadiazol-3-yl	H	5-Cl	F	R
0	pyrimidin-5-yl	5-CH ₃ -1,2,4-oxadiazol-3-yl	H	5-CH ₃	F	R
0	CF ₃	5-CH ₃ -1,2,4-oxadiazol-3-yl	H	5-CH ₃	F	R
0	pyrimidin-5-yl	5-CH ₃ -1,2,4-oxadiazol-3-yl	H	5-F	F	R
0	CF ₃	5-CH ₃ -1,2,4-oxadiazol-3-yl	H	5-F	F	R
0	pyrimidin-5-yl	methoxy	F	5-F	H	R
0	CF ₃	methoxy	F	5-F	H	R
0	pyrimidin-5-yl	2-CH ₃ -2H-tetrazol-5-yl	H	5-F	F	R
0	CF ₃	2-CH ₃ -2H-tetrazol-5-yl	H	5-F	F	R
0	CF ₃	CO ₂ CH ₃	H	5-Cl	F	R
0	CClF ₂	CO ₂ CH ₃	H	5-Cl	F	R
0	CF ₃	CO ₂ CH ₃	H	5-CH ₃	F	R
0	CClF ₂	CO ₂ CH ₃	H	5-CH ₃	F	R
0	CF ₃	3-CH ₃ -1,2,4-oxadiazol-5-yl	H	5-F	F	R
0	CF ₃	3-CH ₃ -1,2,4-oxadiazol-5-yl	H	5-Cl	F	R
0	CClF ₂	3-CH ₃ -1,2,4-oxadiazol-5-yl	H	5-Cl	F	R
0	CF ₃	3-CH ₃ -1,2,4-oxadiazol-5-yl	H	5-CH ₃	F	R
0	CClF ₂	3-CH ₃ -1,2,4-oxadiazol-5-yl	H	5-CH ₃	F	R
0	CF ₃	CO ₂ CH ₃	H	5-F	F	R
0	CClF ₂	CO ₂ CH ₃	H	5-F	F	R
0	pyrimidin-5-yl	2-CH ₃ -2H-tetrazol-5-yl	H	5-Cl	F	R
0	CF ₃	2-CH ₃ -2H-tetrazol-5-yl	H	5-Cl	F	R
0	pyrimidin-5-yl	2-CH ₃ -2H-tetrazol-5-yl	H	5-CH ₃	F	R

m	R5	R6a	R6b	R6c	R7a	*
0	CF ₃	2-CH ₃ -2H-tetrazol-5-yl	H	5-CH ₃	F	R
0	CF ₃	CONHCH ₃	Cl	H	F	R
0	CF ₃	NHCO ₂ CH ₃	Cl	H	F	R
0	CF ₃	NHCO ₂ CH(CH ₃) ₂	Cl	H	F	R
0	pyrimidin-5-yl	NHCO ₂ CH(CH ₃) ₂	Cl	H	F	R
0	CF ₃	NHCO ₂ CH ₃	F	H	F	R
0	CF ₃	2-methoxy-2-oxoethyl	F	H	F	R
0	CF ₃	CONHCH ₃	F	H	F	R
0	CF ₃	CH ₂ OCH ₃	Cl	H	F	R
0	CF ₃	hydroxy	Cl	5-Cl	H	R
0	pyrimidin-5-yl	NHCO ₂ CH ₃	F	H	F	R
0	pyrimidin-5-yl	NHCO ₂ CH ₃	Cl	H	F	R
0	CF ₃	CO ₂ CH ₃	H	6-CH ₃	F	R
0	CClF ₂	CO ₂ CH ₃	H	6-CH ₃	F	R
0	CF ₃	CO ₂ CH ₃	Cl	H	F	R
0	CF ₃	CO ₂ CH ₃	CH ₃	H	F	R
0	CClF ₂	CO ₂ CH ₃	CH ₃	H	F	R
1	pyrimidin-5-yl	CO ₂ CH ₃	F	H	H	§
1	CF ₃	3-CH ₃ -1,2,4-oxadiazol-5-yl	F	H	F	R
1	CClF ₂	3-CH ₃ -1,2,4-oxadiazol-5-yl	F	H	F	R
1	pyrimidin-5-yl	3-CH ₃ -1,2,4-oxadiazol-5-yl	F	H	F	R
1	CF ₃	CO ₂ CH ₃	F	H	F	R
1	CClF ₂	CO ₂ CH ₃	F	H	F	R
1	pyrimidin-5-yl	CO ₂ CH ₃	F	H	F	R
1	pyrimidin-5-yl	CO ₂ CH ₃	F	H	H	R
1	pyrimidin-5-yl	2-CH ₃ -2H-tetrazol-5-yl	F	H	F	R
1	CF ₃	CO ₂ CH ₃	Cl	H	F	R
1	CClF ₂	CO ₂ CH ₃	Cl	H	F	R
1	CHF ₂	CO ₂ CH ₃	Cl	H	F	R

* stereoconfiguration at the indicated carbon,

§ R^{3a} is CH₃

Unless otherwise stated, the following terms have the meanings indicated below:

"Alkyl" as well as other groups having the prefix "alk" such as, for example, alkoxy, alkanoyl, alkenyl, alkynyl and the like, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl and the like.

"Alkenyl" means a linear or branched carbon chain containing at least one C=C bond. Examples of alkenyl include allyl, 2-butenyl, 3-butenyl, 1-methyl-2-propenyl, and the like.

"Alkynyl" means a linear or branched carbon chain containing at least one C≡C bond. Examples of alkynyl include propargyl, 2-butyne, 3-butyne, 1-methyl-2-propynyl, and the like.

"Cyclic imide" includes succinimide, maleimide, phthalimide and the like.

"Cycloalkyl" means carbocycles containing no heteroatoms, and includes mono-, bi- and tricyclic saturated carbocycles, as well as fused ring systems. Such fused ring systems can include one ring that is partially or fully unsaturated such as a benzene ring to form fused ring systems such as benzofused carbocycles. Cycloalkyl includes such fused ring systems as spirofused ring systems. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decahydronaphthalene, adamantane, indanyl, indenyl, fluorenyl, 1,2,3,4-tetrahydronaphthalene and the like.

"Haloalkyl" means an alkyl radical as defined above wherein at least one and up to all of the hydrogen atoms are replaced with a halogen. Examples of such haloalkyl radicals include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl and the like.

"Halogen" means fluorine, chlorine, bromine and iodine.

"Optionally substituted" is intended to include both substituted and unsubstituted. Thus, for example, optionally substituted aryl could represent a pentafluorophenyl or a phenyl ring.

Optical Isomers - Diastereomers - Geometric Isomers - Tautomers

Compounds described herein may contain an asymmetric center and may thus exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centers, they may additionally exist as diastereomers.

5 The present invention includes all such possible stereoisomers as substantially pure resolved enantiomers, racemic mixtures thereof, as well as mixtures of diastereomers. The above Formula I is shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of Formula I and pharmaceutically acceptable salts thereof. Diastereoisomeric pairs of enantiomers

10 may be separated by, for example, fractional crystallization from a suitable solvent, and the pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically active acid or base as a resolving agent or on a chiral HPLC column. Further, any enantiomer or diastereomer of a compound of the general Formula I may be obtained

15 by stereospecific synthesis using optically pure starting materials or reagents of known configuration.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

20 Some of the compounds described herein may exist with different points of attachment of hydrogen, referred to as tautomers. Such an example may be a ketone and its enol form known as keto-enol tautomers. The individual tautomers as well as mixture thereof are encompassed with compounds of Formula I.

25 Salts

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and

30 organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric, ferrous, lithium, magnesium, manganese (ic and ous), potassium, sodium, zinc and the like salts. Preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts prepared from pharmaceutically acceptable organic non-toxic bases include salts of primary,

secondary, and tertiary amines derived from both naturally occurring and synthetic sources. Pharmaceutically acceptable organic non-toxic bases from which salts can be formed include, for example, arginine, betaine, caffeine, choline, N,N'-dibenzyl-ethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, dicyclohexylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

Prodrugs

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds of this invention which are readily convertible in vivo into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various conditions described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound in vivo after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs," ed. H. Bundgaard, Elsevier, 1985. Metabolites of these compounds include active species produced upon introduction of compounds of this invention into the biological milieu.

Pharmaceutical Compositions

Another aspect of the present invention provides pharmaceutical compositions which comprises a compound of Formula I and a pharmaceutically

acceptable carrier. The term "composition", as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) (pharmaceutically acceptable excipients) that make up the carrier, as well as any product which results, directly or indirectly, from combination, 5 complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of Formula I, additional active ingredient(s), and pharmaceutically 10 acceptable excipients.

The pharmaceutical compositions of the present invention comprise a compound represented by Formula I (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier and optionally other therapeutic ingredients or adjuvants. The compositions include compositions suitable 15 for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well 20 known in the art of pharmacy.

In practice, the compounds represented by Formula I, or pharmaceutically acceptable salts thereof, of this invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide 25 variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as 30 granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compound represented by Formula I, or pharmaceutically acceptable salts thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of

the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

Thus, the pharmaceutical compositions of this invention may include a pharmaceutically acceptable carrier and a compound or a pharmaceutically acceptable salt of Formula I. The compounds of Formula I, or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.1mg to about 500mg of the active ingredient and

each cachet or capsule preferably containing from about 0.1mg to about 500mg of the active ingredient.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, utilizing a compound represented by Formula I of this invention, or pharmaceutically acceptable salts thereof, via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in moulds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or

more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a
 5 compound described by Formula I, or pharmaceutically acceptable salts thereof, may also be prepared in powder or liquid concentrate form.

The following are examples of representative pharmaceutical dosage forms for the compounds of Formula I:

10 Injectable Suspension (I.M.) mg/mL

Compound of Formula I	10
Methylcellulose	5.0
Tween 80	0.5
Benzyl alcohol	9.0
15 Benzalkonium chloride	1.0
Water for injection to a total volume of 1 mL	

<u>Tablet</u>	<u>mg/tablet</u>
Compound of Formula I	25
20 Microcrystalline Cellulose	415
Povidone	14.0
Pregelatinized Starch	43.5
Magnesium Stearate	2.5
	500

<u>Capsule</u>	<u>mg/capsule</u>
Compound of Formula I	25
Lactose Powder	573.5
Magnesium Stearate	1.5
25	
30	600

Utilities

Compounds of this invention are antagonists or inverse agonists of bradykinin receptor, in particular the bradykinin B1 receptor, and as such are useful in
 35 the treatment and prevention of diseases and conditions mediated through the

bradykinin receptor pathway such as pain and inflammation. The compounds would be effective in the treatment or prevention of pain including, for example, visceral pain (such as pancreatitis, interstitial cystitis, renal colic), neuropathic pain (such as postherpetic neuralgia, nerve injury, the "dynias", e.g., vulvodynia, phantom limb
5 pain, root avulsions, painful traumatic mononeuropathy, painful polyneuropathy), central pain syndromes (potentially caused by virtually any lesion at any level of the nervous system), and postsurgical pain syndromes (eg, postmastectomy syndrome, postthoracotomy syndrome, stump pain)), bone and joint pain (osteoarthritis), repetitive motion pain, dental pain, cancer pain, myofascial pain (muscular injury,
10 fibromyalgia), perioperative pain (general surgery, gynecological), chronic pain, dysmenorrhea, as well as pain associated with angina, and inflammatory pain of varied origins (e.g. osteoarthritis, rheumatoid arthritis, rheumatic disease, teno-synovitis and gout).

Further, the compounds of this invention can also be used to treat
15 hyperreactive airways and to treat inflammatory events associated with airways disease e.g. asthma including allergic asthma (atopic or non-atopic) as well as exercise-induced bronchoconstriction, occupational asthma, viral- or bacterial exacerbation of asthma, other non-allergic asthmas and "wheezy-infant syndrome". Compounds of the present invention may also be used to treat chronic obstructive
20 pulmonary disease including emphysema, adult respiratory distress syndrome, bronchitis, pneumonia, allergic rhinitis (seasonal and perennial), and vasomotor rhinitis. They may also be effective against pneumoconiosis, including aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis.

Compounds of the present invention may also be used for the treatment
25 of inflammatory bowel disease including Crohn's disease and ulcerative colitis, irritable bowel syndrome, pancreatitis, nephritis, cystitis (interstitial cystitis), uveitis, inflammatory skin disorders such as psoriasis and eczema, rheumatoid arthritis and edema resulting from trauma associated with burns, sprains or fracture, cerebral
30 edema and angioedema. They may be used to treat diabetic vasculopathy, diabetic neuropathy, diabetic retinopathy, post capillary resistance or diabetic symptoms associated with insulinitis (e.g. hyperglycemia, diuresis, proteinuria and increased nitrite and kallikrein urinary excretion). They may be used as smooth muscle relaxants for the treatment of spasm of the gastrointestinal tract or uterus. Additionally, they may
35 be effective against liver disease, multiple sclerosis, cardiovascular disease, e.g.

atherosclerosis, congestive heart failure, myocardial infarct; neurodegenerative diseases, eg. Parkinson's and Alzheimers disease, epilepsy, septic shock e.g. as anti-hypovolemic and/or anti-hypotensive agents, headache including cluster headache, migraine including prophylactic and acute use, closed head trauma, cancer, sepsis, gingivitis, osteoporosis, benign prostatic hyperplasia and hyperactive bladder. Animal models of these diseases and conditions are generally well known in the art, and may be suitable for evaluating compounds of the present invention for their potential utilities. Finally, compounds of the present invention are also useful as research tools (*in vivo* and *in vitro*).

10 The compounds of this invention are useful in the treatment of pain and inflammation by the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or
15 three times a week.

 The compounds would be effective in the treatment or prevention of pain including, for example, bone and joint pain (osteoarthritis), repetitive motion pain, dental pain, cancer pain, myofascial pain (muscular injury, fibromyalgia), perioperative pain (general surgery, gynecological) and chronic pain by the
20 administration of a tablet, cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or three times a week.

 In particular, inflammatory pain such as, for example, inflammatory
25 airways disease (chronic obstructive pulmonary disease) would be effectively treated by the compounds of this invention by the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release
30 formulation) once, twice or three times a week.

 Further, the compounds of this invention can additionally be used to treat asthma, inflammatory bowel disease, rhinitis, pancreatitis, cystitis (interstitial cystitis), uveitis, inflammatory skin disorders, rheumatoid arthritis and edema resulting from trauma associated with burns, sprains or fracture by the administration
35 of a tablet, cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg,

5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or three times a week.

They may be used subsequent to surgical intervention (e.g. as post-operative analgesics) and to treat inflammatory pain of varied origins (e.g. osteoarthritis, rheumatoid arthritis, rheumatic disease, teno-synovitis and gout) as well as for the treatment of pain associated with angina, menstruation or cancer by the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or three times a week.

They may be used to treat diabetic vasculopathy, post capillary resistance or diabetic symptoms associated with insulinitis (e.g. hyperglycemia, diuresis, proteinuria and increased nitrite and kallikrein urinary excretion) by the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or three times a week.

They may be used to treat inflammatory skin disorders such as psoriasis and eczema by the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or three times a week.

They may be used as smooth muscle relaxants for the treatment of spasm of the gastrointestinal tract or uterus or in the therapy of Crohn's disease, ulcerative colitis or pancreatitis by the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or three times a week.

Such compounds may be used therapeutically to treat hyperreactive airways and to treat inflammatory events associated with airways disease e.g. asthma, and to control, restrict or reverse airways hyperreactivity in asthma by the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg,

0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or three times a week.

They may be used to treat intrinsic and extrinsic asthma including
5 allergic asthma (atopic or non-atopic) as well as exercise-induced broncho-
constriction, occupational asthma, viral or bacterial exacerbated asthma, other non-
allergic asthmas and "wheezy-infant syndrome" by the administration of a tablet,
cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg,
10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this
10 invention once every three to four hours, once, twice or three times a day, or (in an
extended release formulation) once, twice or three times a week.

They may also be effective against pneumoconiosis, including
aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis
and byssinosis as well as adult respiratory distress syndrome, chronic obstructive
15 pulmonary or airways disease, bronchitis, allergic rhinitis, and vasomotor rhinitis by
the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg,
0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a
compound of this invention once every three to four hours, once, twice or three times
a day, or (in an extended release formulation) once, twice or three times a week.

20 Additionally, they may be effective against liver disease, multiple
sclerosis, atherosclerosis, Alzheimer's disease, septic shock e.g. as anti-hypovolemic
and/or anti-hypotensive agents, cerebral edema, headache including cluster headache,
migraine including prophylactic and acute use, closed head trauma, irritable bowel
syndrome and nephritis by the administration of a tablet, cachet, or capsule each
25 containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg,
125mg, 250mg, or 500mg of a compound of this invention once every three to four
hours, once, twice or three times a day, or (in an extended release formulation) once,
twice or three times a week.

30 Combination Therapy

Compounds of Formula I may be used in combination with other drugs
that are used in the treatment/prevention/suppression or amelioration of the diseases
or conditions for which compounds of Formula I are useful. Such other drugs may be
administered, by a route and in an amount commonly used therefor,
35 contemporaneously or sequentially with a compound of Formula I. When a

compound of Formula I is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of Formula I is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of Formula I. Examples of other active ingredients that may be combined with a compound of Formula I, either administered separately or in the same pharmaceutical compositions, include, but are not limited to:

(1) morphine and other opiate receptor agonists including propoxyphene (Darvon); (2) non-steroidal antiinflammatory drugs (NSAIDs) including COX-2 inhibitors such as propionic acid derivatives (alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, fluprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, piroprofen, pranoprofen, suprofen, tiaprofenic acid, and tioxaprofen), acetic acid derivatives (indomethacin, acemetacin, alclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin, and zomepirac), fenamic acid derivatives (flufenamic acid, meclofenamic acid, mefenamic acid, niflumic acid and tolfenamic acid), biphenylcarboxylic acid derivatives (diflunisal and flufenisal), oxicams (isoxicam, piroxicam, sudoxicam and tenoxicam), salicylates (acetyl salicylic acid, sulfasalazine) and the pyrazolones (apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone, phenylbutazone), and the coxibs (celecoxib, valecoxib, rofecoxib and etoricoxib); (3) corticosteroids such as betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone and triamcinolone; (4) histamine H1 receptor antagonists such as bromopheniramine, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripeleminamine, hydroxyzine, methdilazine, promethazine, trimeprazine, azatadine, cyproheptadine, antazoline, pheniramine pyrilamine, astemizole, terfenadine, loratadine, cetirizine, desloratadine, fexofenadine and levocetirizine; (5) histamine H2 receptor antagonists such as cimetidine, famotidine and ranitidine; (6) proton pump inhibitors such as omeprazole, pantoprazole and esomeprazole; (7) leukotriene antagonists and 5-lipoxygenase inhibitors such as zafirlukast, montelukast, pranlukast and zileuton; (8) drugs used for angina, myocardial ischemia including nitrates such as nitroglycerin and isosorbide nitrates, beta blockers such as atenolol, metoprolol, propranolol, acebutolol, betaxolol, bisoprolol, carteolol, labetalol, nadolol, oxprenolol, penbutolol, pindolol, sotalol and timolol, and calcium channel blockers such as diltiazam, verapamil, nifedipine,

- bepidil, felodipine, flunarizine, isradipine, nicardipine and nimodipine; (9) incontinence medications such as antimuscarinics, e.g., tolterodine and oxybutinin); (10) gastrointestinal antispasmodics (such as atropine, scopolamine, dicyclomine, antimuscarinics, as well as diphenoxylate); skeletal muscle relaxants
- 5 (cyclobenzaprine, carisoprodol, chlorphenesin, chlorzoxazone, metaxalone, methocarbamol, baclofen, dantrolene, diazepam, or orphenadrine); (11) gout medications such as allopurinol, probenecid and colchicine; (12) drugs for rheumatoid arthritis such as methotrexate, auranofin, aurothioglucose and gold sodium thiomalate; (13) drugs for osteoporosis such as alendronate and raloxifene;
- 10 decongestants such as pseudoephedrine and phenylpropanolamine; (14) local anesthetics; (15) anti-herpes drugs such as acyclovir, valacyclovir and famcyclovir; and (15) anti-emetics such as ondansetron and granisetron.

Biological Evaluation

- 15 Assessing the Affinity of Selected Compounds to Bind to the Bradykinin B1 or B2 Receptor

Radioligand binding assays are performed using membranes from CHO cells that stably express the human, rabbit, rat, or dog B1 receptors or CHO cells that express the human B2 receptor. For all receptor types, cells are harvested from

20 culture flasks in PBS/1mM EDTA and centrifuged at 1000xg for 10 minutes. The cell pellets are homogenized with a polytron in ice cold 20mM HEPES, 1mM EDTA, pH 7.4 (lysis buffer) and centrifuged at 20,000xg for 20 minutes. The membrane pellets are rehomogenized in lysis buffer, centrifuged again at 20,000xg and the final pellets are resuspended at 5mg protein/ml in assay buffer (120mM NaCl, 5mM KCl, 20mM

25 HEPES, pH 7.4) supplemented with 1% BSA and frozen at -80°C.

On the day of assay, membranes are centrifuged at 14,000xg for 5 minutes and resuspended to the desired protein concentration in assay buffer containing 100nM enalaprilat, 140µg/mL bacitracin and 0.1% BSA. 3H-des-arg10, leu9 kallidin is the radioligand used for the human and rabbit B1 receptors, 3H-des-

30 arg10 kallidin is used for the rat and dog B1 receptors, and 3H-bradykinin is used to label the human B2 receptor.

For all assays, compounds are diluted from DMSO stock solutions with 4µL added to assay tubes for a final DMSO concentration of 2%. This is followed by the addition of 100µL radioligand and 100µL of the membrane

35 suspension. Nonspecific binding for the B1 receptor binding assays is determined

using 1 μ M des-arg¹⁰ kallidin and nonspecific binding for the B2 receptor is determined with 1 μ M bradykinin. Tubes are incubated at room temperature (22°C) for 60 minutes followed by filtration using a Tomtec 96-well harvesting system. Radioactivity retained by the filter is counted using a Wallac Beta-plate scintillation counter.

The compounds of this invention have affinity for the B1 receptor in the above assay as demonstrated by results of less than 5 μ M. It is advantageous that the assay results be less than 1 μ M, even more advantageous for the results be less than 0.5 μ M. It is further advantageous that compounds of this invention have affinity for the bradykinin B1 receptor over the bradykinin B2 receptor; more advantageously, the affinity for the B1 receptor is at least 10 fold, and preferably over 100 fold, over that for the B2 receptor.

Assay for Bradykinin B1 Antagonists

B1 agonist-induced calcium mobilization was monitored using a Fluorescence Imaging Plate Reader (FLIPR). CHO cells expressing the B1 receptor were plated in 96 or 384 well plates and allowed to incubate in Iscove's modified DMEM overnight. Wells were washed two times with a physiological buffered salt solution and then incubated with 4 μ M Fluo-3 for one hour at 37°C. The plates were then washed two times with buffered salt solution and 100 μ L of buffer was added to each well. Plates were placed in the FLIPR unit and allowed to equilibrate for two minutes. The test compound was then added in 50 μ L volumes followed five minutes later by 50 μ L of agonist (des-arg¹⁰ kallidin). Relative fluorescence peak heights in the absence and presence of antagonist were used to calculate the degree of inhibition of the B1 receptor agonist response by the test compound. Eight to ten concentrations of test compound were typically evaluated to construct an inhibition curve and determine IC₅₀ values using a four-parameter nonlinear regression curve fitting routine.

Assay for Bradykinin Inverse Agonists

Inverse agonist activity at the human B1 receptor was evaluated using transiently transfected HEK293 cells. One day following transfection cell flasks were labeled overnight with 6 μ Ci/ml [³H]myo-inositol. On the day of assay, the media was removed and the attached cells were gently rinsed with 2x20ml of phosphate-buffered saline. Assay buffer (HEPES buffered physiological salts, pH 7.4) was added and the cells were detached by tapping of the flask. The cells were centrifuged at 800xg for

five minutes and resuspended at 1×10^6 cells/ml in assay buffer supplemented with 10mM lithium chloride. After 10 minutes at room temperature, one-half ml aliquots were distributed to tubes containing test compound or vehicle. After an additional 10 minutes the tubes were transferred to a 37°C water bath for 30 minutes. The incubation was terminated by the addition of a 12% perchloric acid solution and the tubes were placed on ice for 30 minutes. The acid was then neutralized with KOH and the tubes centrifuged to pellet precipitated material. [^3H]Inositol monophosphate formed was recovered by standard ion exchange chromatographic techniques and quantitated by liquid scintillation counting. Inverse agonist activity was determined by the degree to which a test compound reduced basal (cells incubated with vehicle) levels of [^3H]inositol monophosphate accumulation.

Abbreviations Used

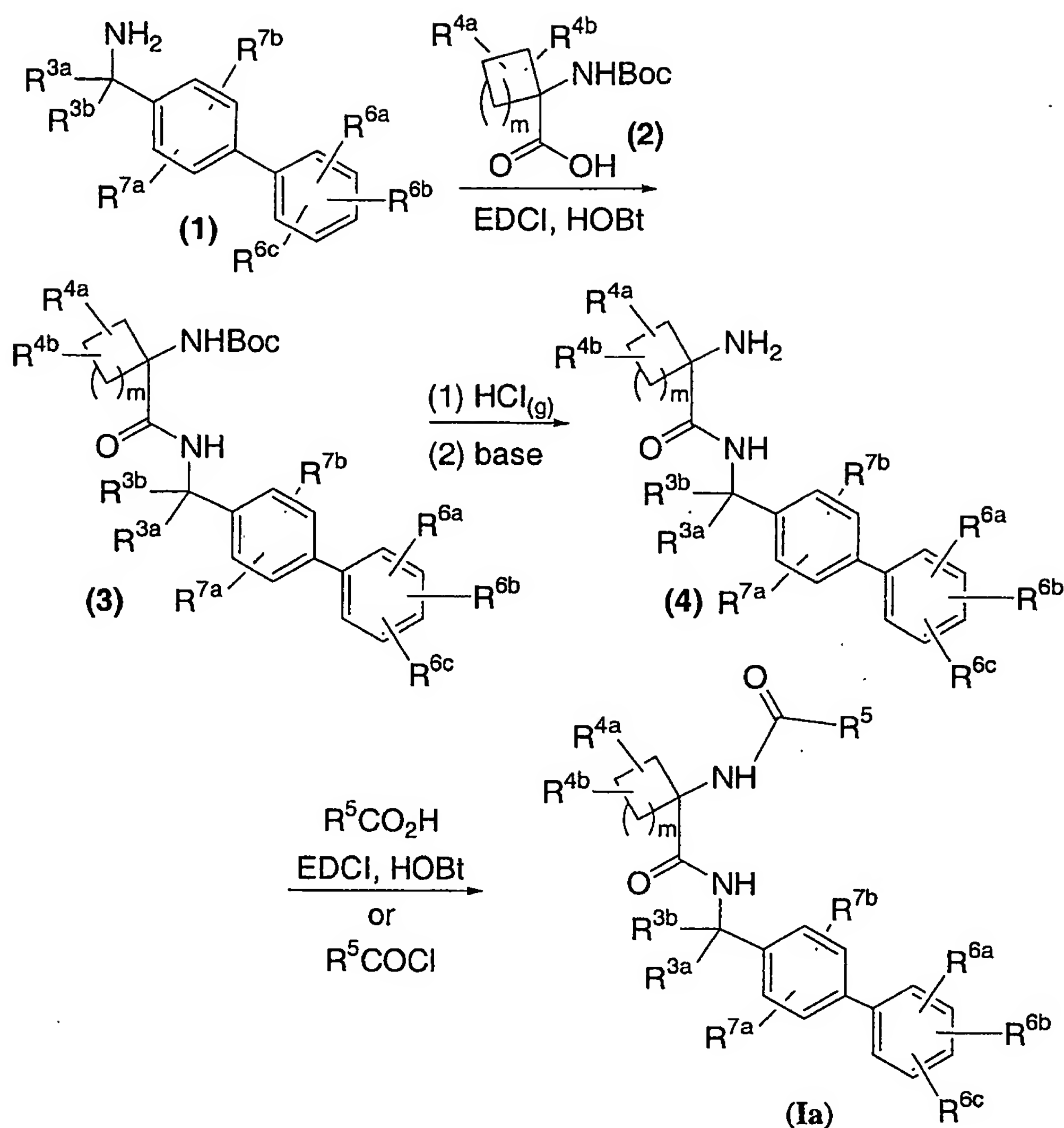
The following abbreviations have the meanings indicated, unless stated otherwise in the specification:

BOC (boc)	t-butyloxycarbonyl
DCM	dichloromethane
DMF	dimethylformamide
DMSO	Dimethyl sulfoxide
EDC or EDCI	1-(3-dimethylaminopropyl)3-ethylcarbodiimide HCl
eq.	equivalent(s)
ES (or ESI) - MS	electron spray ionization - mass spectroscopy
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
FAB-MS	fast atom bombardment-mass spectroscopy
HOBt	1-hydroxybenzotriazole hydrate
HPLC	high pressure liquid chromatography
LCMS	Liquid chromatography/mass spectroscopy
LHMDS	lithium bis(trimethylsilyl)amide
Me	methyl
MeOH	Methanol
MHz	megahertz
MsCl	Mesyl chloride

NEt ₃	Triethylamine
NMR	nuclear magnetic resonance
TFA	trifluoroacetic acid
THF	tetrahydrofuran

Compounds of formula I may be prepared according to the following illustrative schemes.

SCHEME 1



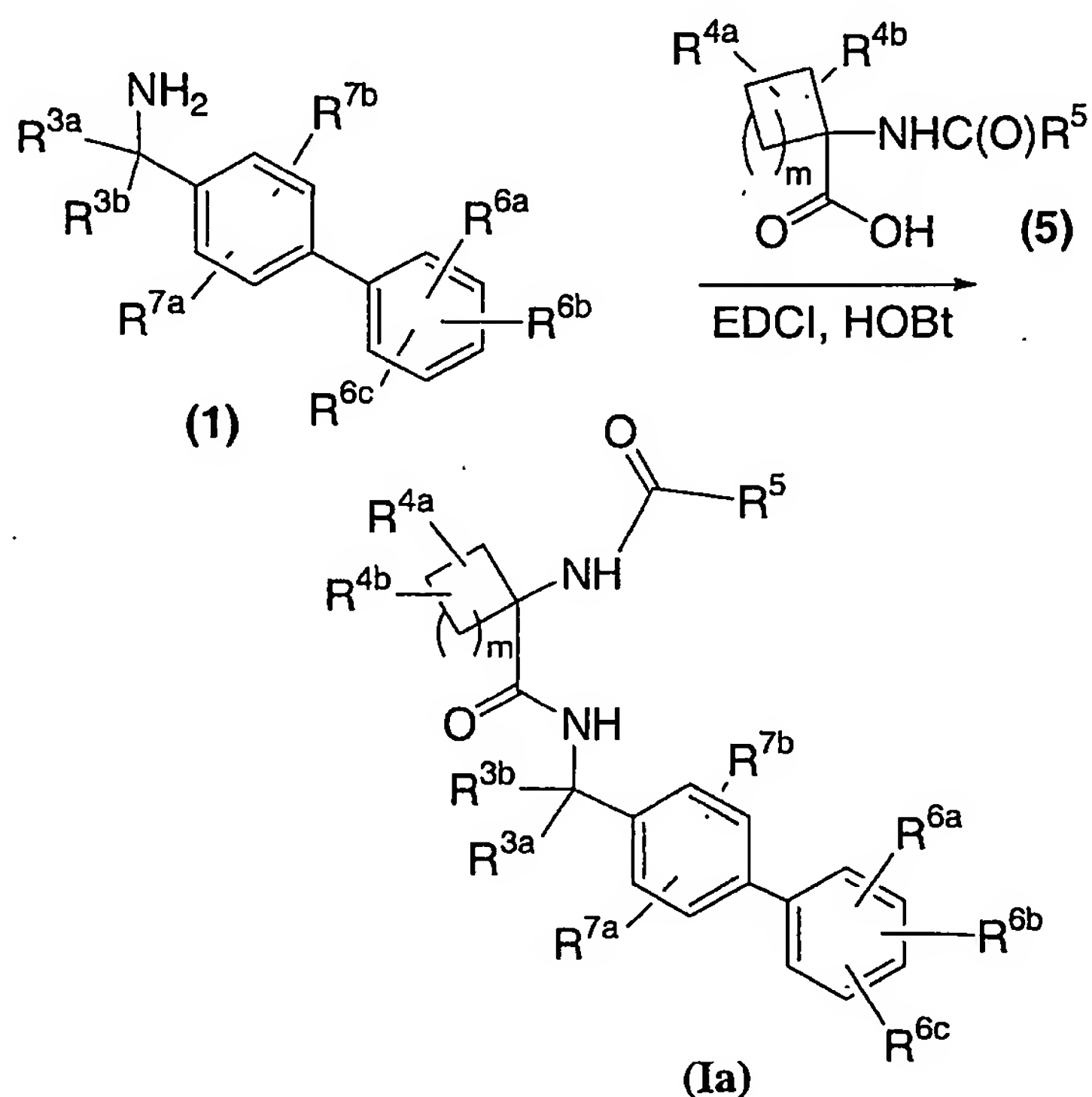
- 5 In Scheme 1, compound (Ia) is assembled by coupling the
 biarylmethanamine derivative (1) to the protected aminocycloalkanoic acid (2) using
 standard peptide coupling reagent combinations, such as EDCI/HOBt, in an
 appropriate solvent, such as THF, to provide (3). The Boc protecting group is then
 removed by the action of an acid, like HCl, in an appropriate solvent, like MeOH, to
 10 yield an ammonium salt from which the free-base derivative (4) may be obtained
 using an appropriate base, such as ammonia, and an appropriate solvent, such as

chloroform. This amine derivative (4) is then reacted with a carboxylic acid or carboxylic acid equivalent to yield title compound (Ia). Alternatively, the acid-salt of (4) can be used in the final reaction to yield title compound (Ia) provided an appropriate base such as triethylamine is added.

5 Alternatively, compound (Ia) may be assembled by coupling the biarylmethanamine derivative (1), with the acylated aminocycloalkanoic acid (5) as shown in Scheme 1a.

SCHEME 1a

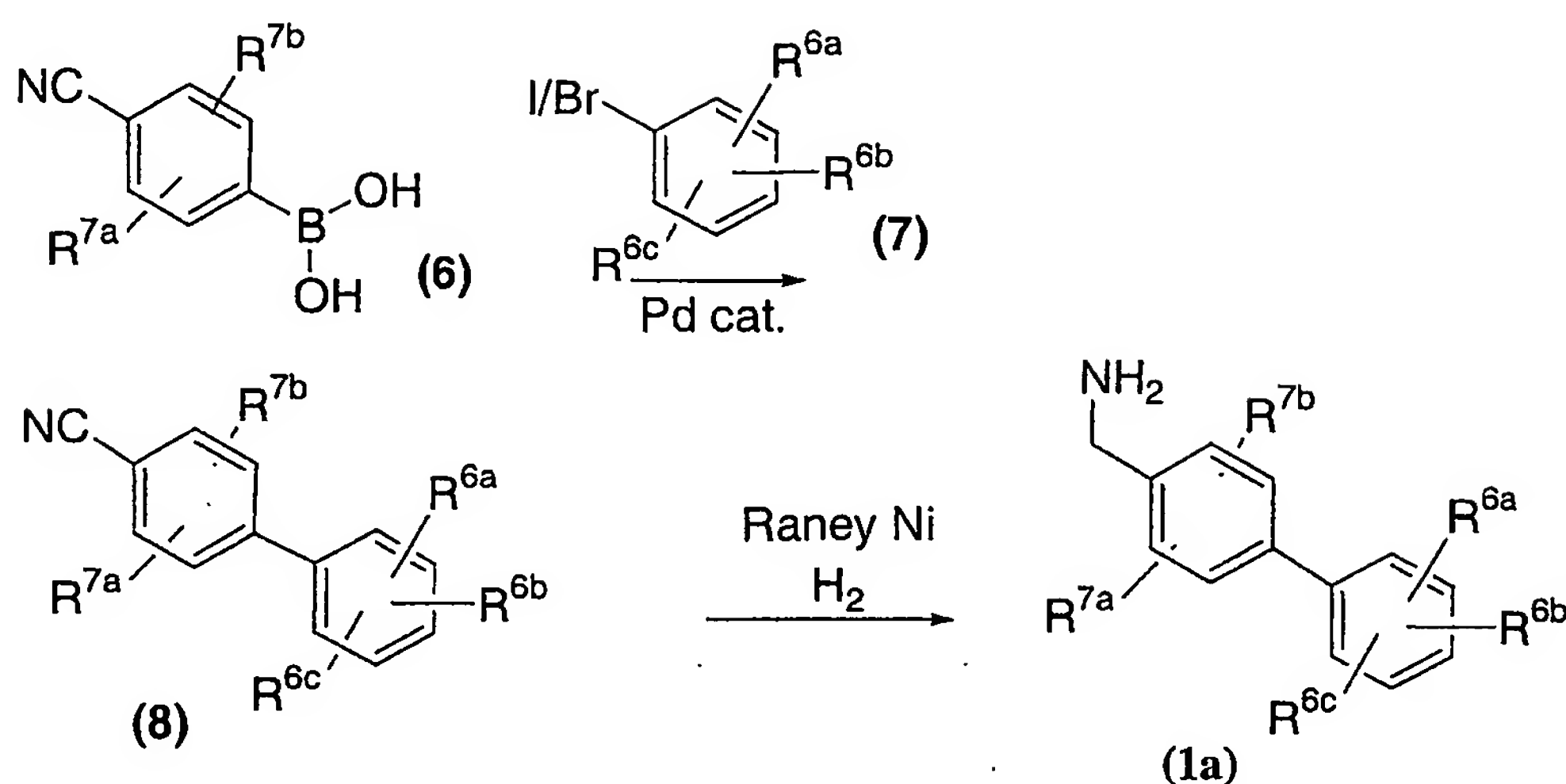
10



A number of synthetic strategies may be employed to assemble the intermediate biarylmethanamine derivative (1) as shown in Schemes 2a-2c.

15

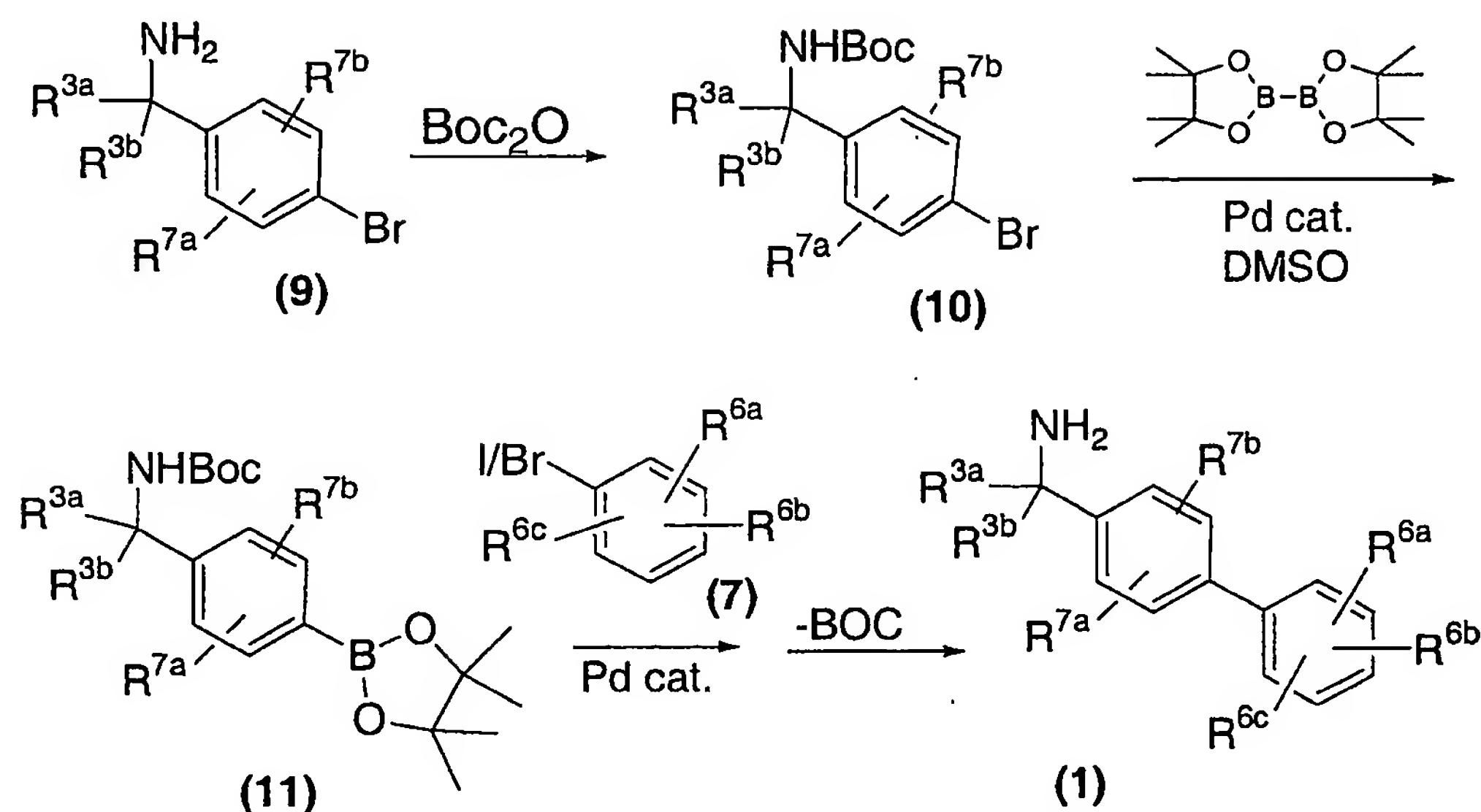
SCHEME 2a



5 In Scheme 2a, the cyanobiaryl derivative (8) is assembled using a Suzuki reaction between an aromatic boronic acid derivative (6), or an appropriate boronic ester derivative, and an aromatic halide (7) in the presence of a triarylphosphine, like triphenylphosphine, and a metal catalyst, like palladium acetate. The resultant cyano biaryl intermediate (8) is then catalytically reduced to the
 10 corresponding amine biaryl derivative (1a) using hydrogen and a metal, such as Raney Ni, in an appropriate solvent.

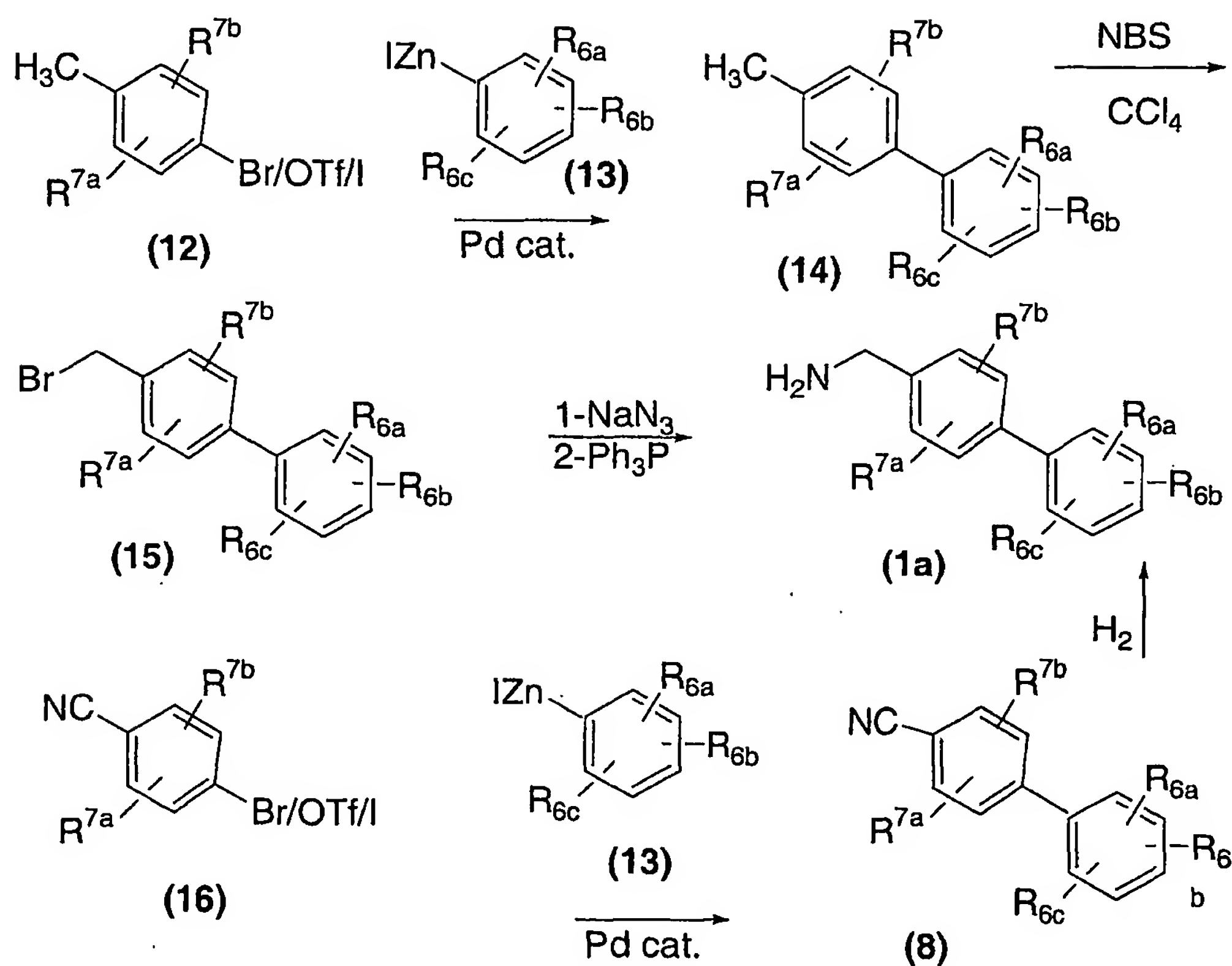
Alternatively, as illustrated in Scheme 2b, a methanamine derivative (9), after primary amine protection with an appropriate protecting group such as Boc, is elaborated to the pinacol boron ester (11) using a palladium catalyst in an
 15 appropriate solvent, like dimethyl sulfoxide. This boron ester (11) is coupled to an aryl halide derivative (7) employing Suzuki reaction conditions to yield (1).

SCHEME 2b



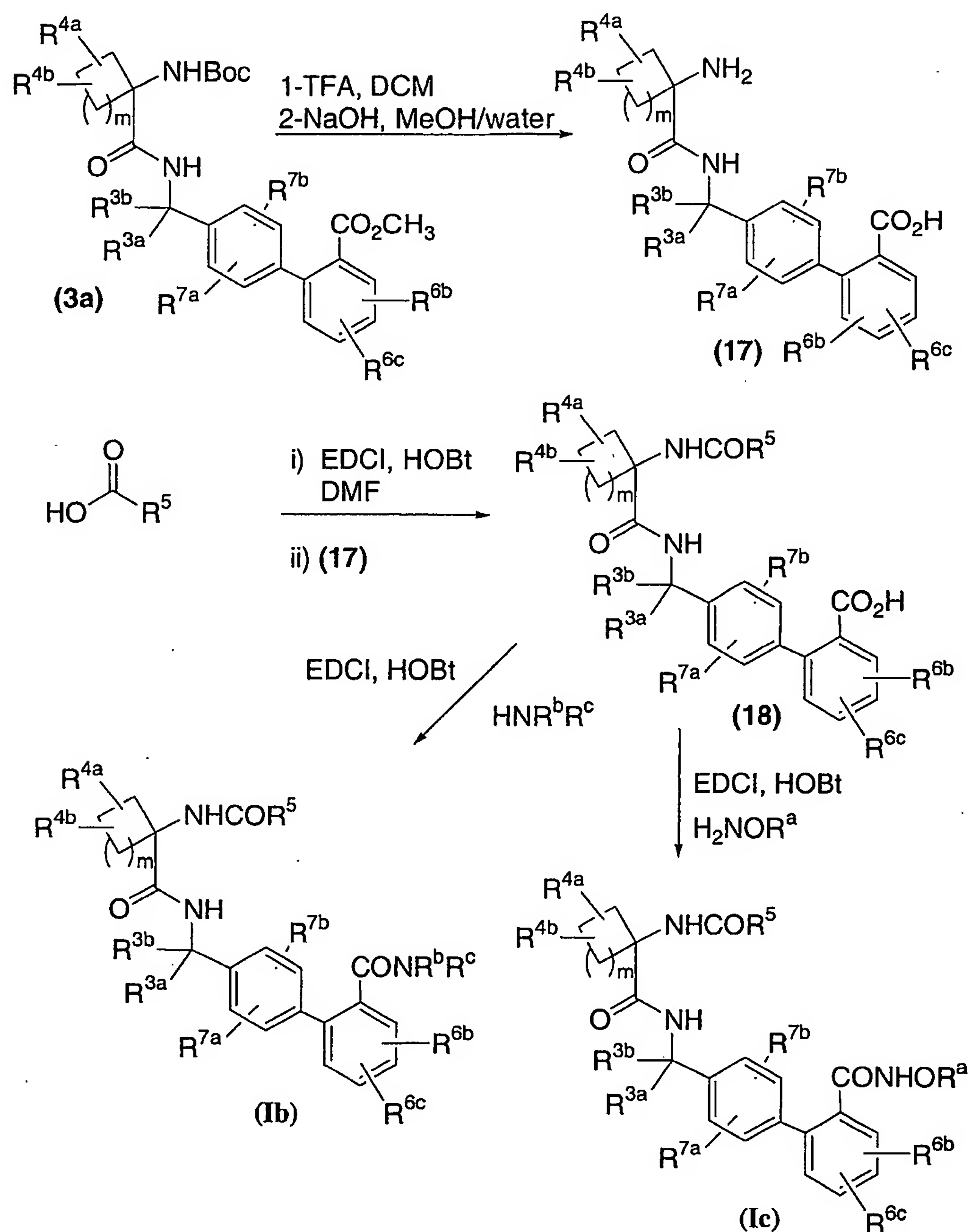
- 5 A third method for the preparation of biarylmethanamine derivatives is depicted in Scheme 2c. The biaryl moiety (14) is first assembled using a palladium catalyzed coupling of (12) with an aryl zinc compound (13) as shown. The methyl group of biaryl (14) is then elaborated according to the three step sequence of
- 10 halogenation, nucleophilic displacement of the halogen with azide, and reduction to provide the corresponding amine intermediate (1a). Alternatively, the biarylmethanamine (1a) can also be prepared starting from the arylcarbonitrile (16) and aryl zinc compound (13) as previously discussed. The resulting biarylcarbonitrile (8) is then reduced using hydrogen to provide (1a).

SCHEME 2c



- 5 It will be appreciated by persons skilled in the art that functional group interconversion can be used to provide various compounds of formula I. As illustrated in Scheme 3, derivative (3a) is bis-protected first by the action of a strong acid, like TFA, and second by alkaline hydrolysis in a suitable mixture of water and an organic solvent, like methanol, at a temperature between 25 and 100 °C to
- 10 yield the amino acid derivative (17). Prior activation of a carboxylic acid (R^5COOH) with an appropriate set of peptide coupling reagents, like EDCI/HOBt, forms the 'active ester' which then reacts with the amino acid derivative (17) to yield (18). The latter compound can either react with amines (HNR^bR^c) or alkyloxy amines (H_2NOR^a) under the action of an appropriate set of peptide coupling reagents, like
- 15 EDCI/HOBt, to form the claimed compounds (Ib) and (Ic), respectively.

SCHEME 3



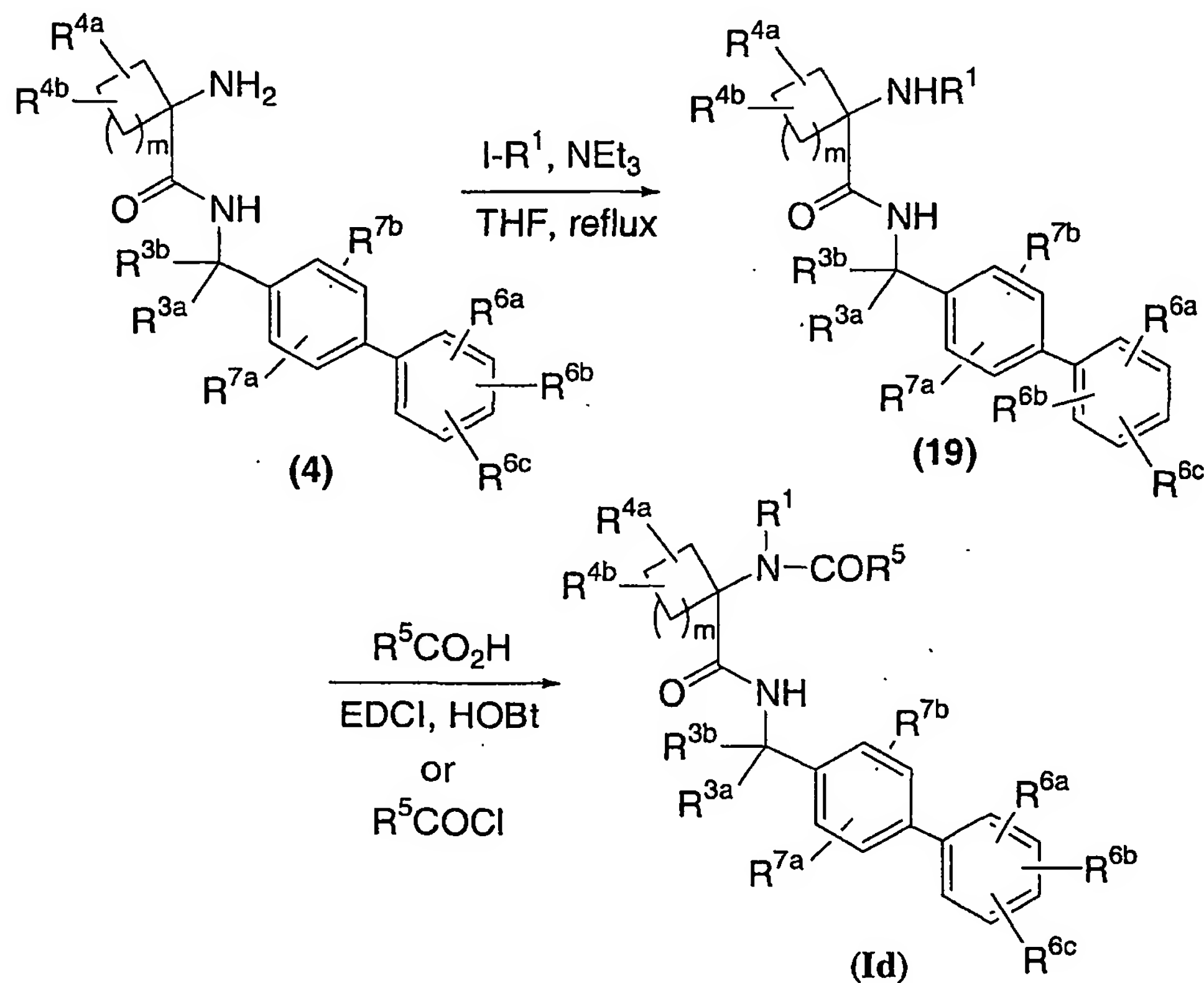
5

N-alkylation is illustrated in Scheme 4. The amine (4) is alkylated with excess alkyl iodide ($I-R^1$) in an appropriate solvent, like THF, in the presence of

an acid scavenger, like triethylamine, at elevated temperatures to provide (19), along with bis-alkylated material. Secondary amine (19) is then converted to the title compound by reacting with a carboxylic acid or carboxylic acid equivalent to provide (Id).

5

SCHEME 4



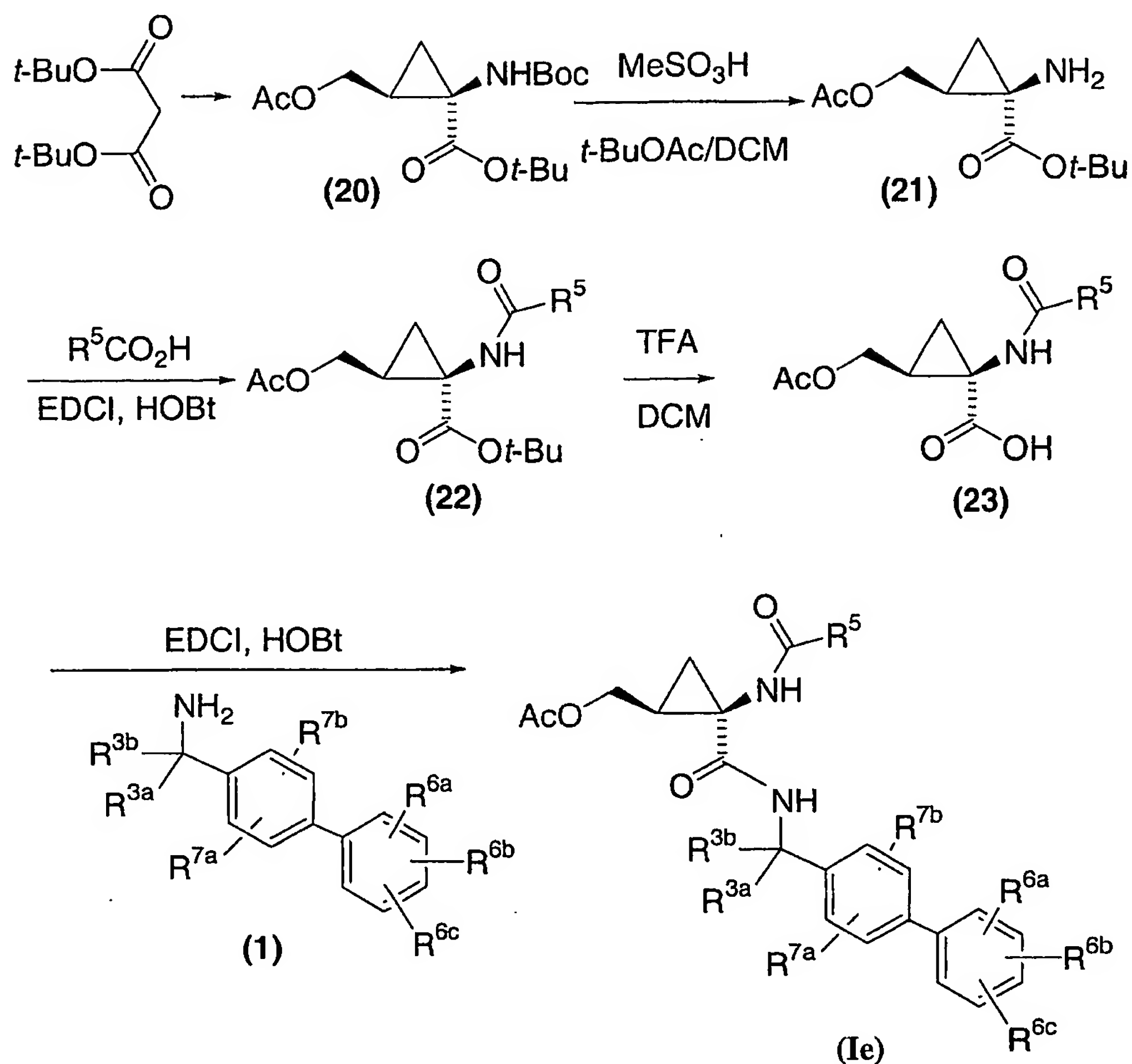
10

The preparation of compounds of formula I having a 1,2-cis- or 1,2-trans-cyclopropyl moiety is illustrated in Schemes 5 and 6. According to known procedures (K. Burgess et al., *J. Org. Chem.*, 57:5931-5936(1992)), di-*tert*-butyl malonate is elaborated to derivative (20). The N-Boc group is removed using methane sulfonic acid according to L. S. Lin et al. *Tetrahedron Lett.*, 41:7013-7016(2000) to give amine (21). This amine is allowed to react with a carboxylic acid or carboxylic acid equivalent under appropriate peptide coupling conditions to yield (22). The *tert*-butyl ester is then cleaved with an acid, like TFA, in an appropriate solvent, like DCM, to provide acid (23). Biarylmethanamine (1) is then coupled with the acid (23)

15

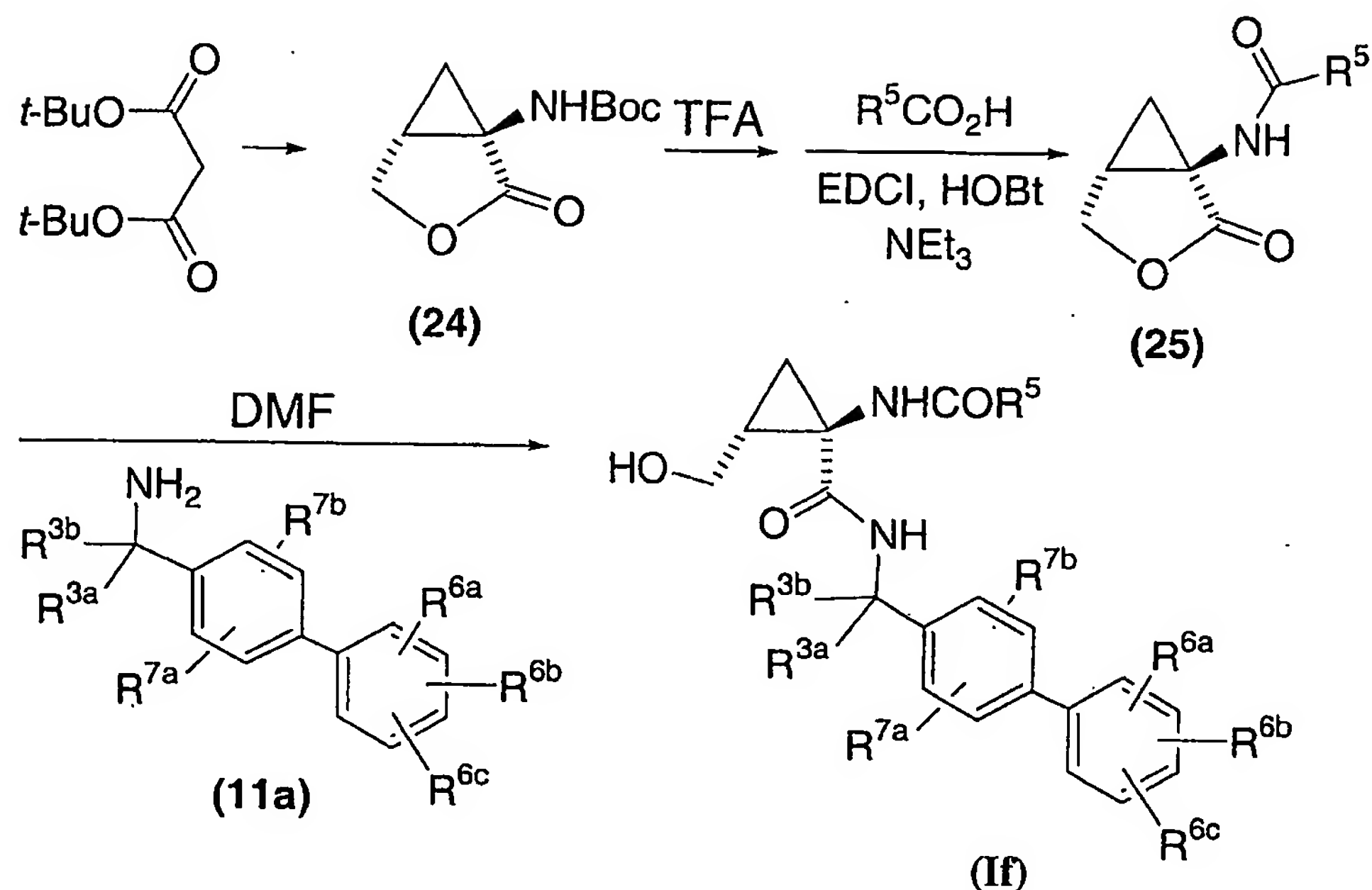
using an appropriate set of peptide coupling reagents, like EDCI/HOBt, to produce the title compound (Ie). Further elaboration of (Ie) to additional compounds of formula I may be accomplished using procedures well known to those skilled in the art. For example, the acetyl group may be removed by hydrolysis to provide the corresponding
5 alcohol; the alcohol may be converted to the corresponding sulfonate by treatment with sulfonyl chloride, and the sulfonate may be converted to the corresponding halide by treatment with a source of the halide. These and other functional transformations to provide compounds of formula I are described in typical organic chemistry textbooks such as March's Advanced Organic Chemistry: Reactions,
10 Mechanisms, and Structure, 5th Ed., John Wiley & Sons, 2000.

SCHEME 5



- 5 In Scheme 6, according to known procedures (K. Burgess et al., *J. Org. Chem.*, 57:5931-5936(1992)), di-*tert*-butyl malonate is elaborated to derivative (24). The N-Boc group is removed using an acid, like TFA, in an appropriate solvent, like DCM. This amine is allowed to react with a carboxylic acid or carboxylic acid equivalent under appropriate peptide coupling conditions, like EDCI/HOBt/NEt₃ to
- 10 yield (25). Biarylmethanamine (1), is then allowed to open the lactone (25) in an appropriate aprotic solvent, like DMF, at a temperature between 20 and 100 °C, to produce the title compound (If). Further elaboration of (If) to additional title compounds may be accomplished using procedures well known to those skilled in the art as previously discussed.

SCHEME 6



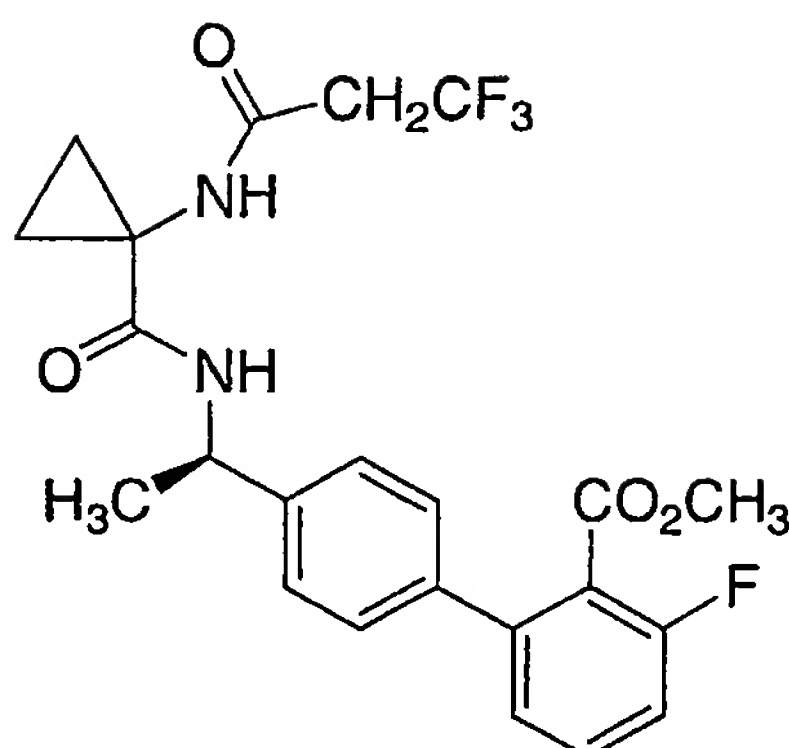
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The following examples are provided to illustrate the invention without limiting the invention to the particulars of these examples. Compounds were named using: ACD/Name version 4.53 (Advanced Chemistry Development Inc. © 1994-2000). Address: 90 Adelaide Street West, Toronto, Ontario, M5H 3V9, Canada.

10

EXAMPLE 1

Methyl 3-fluoro-4'--((1R)-1-[(1-[(3,3,3-trifluoropropanoyl)amino]cyclopropyl)-carbonyl)amino]ethyl)-1,1'-biphenyl-2-carboxylate



Commercially available (1R)-1-(4-bromophenyl)ethanamine was Boc protected, using standard procedures known to those skilled in the art, to produce *tert*-butyl (1R)-1-(4-bromophenyl)ethylcarbamate.

- 5 To a solution of *tert*-butyl (1R)-1-(4-bromophenyl)ethylcarbamate (7.6 g, 25.3 mmol) in DMSO (20 mL) was added bis(pinacolato)diboron (7.07 g, 27.9 mmol), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (2.06 g, 2.53 mmol), and potassium acetate (7.45 g, 76.0 mmol) at room temperature under N₂. The resulting mixture was heated at 80 °C for 1 hour.
- 10 The reaction was quenched by addition of EtOAc and filtered through celite. The organic extract was washed with water three times, saturated NaCl, dried over MgSO₄, filtered and concentrated under vacuum. The residue was purified on silica gel eluted with 0-20% ethyl acetate in hexane to provide *tert*-butyl (1R)-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethylcarbamate as a clear light yellow oil
- 15 with a mass ion (ES⁺) of 333.

- To a stirred solution of *tert*-butyl (1R)-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethylcarbamate (1.0 g, 2.9 mmol) and methyl 2-fluoro-6-iodobenzoate (1.2 g, 4.32 mmol) in 25 mL of a 5:1 THF:water mixture was added potassium carbonate (1.2 g, 8.64 mmol), tri-*o*-tolylphosphine (350 mg, 1.15 mmol)
- 20 and lastly palladium acetate (65 mg, 0.29 mmol). The reaction vessel was then sealed and placed into a 90 °C oil bath for overnight stirring and heating. After about 18 hours the reaction mixture was cooled to ambient temperature and then diluted with EtOAc. The organics were washed with brine (x4), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give an oil. This oil was subject
- 25 to silica gel chromatography eluting with 10-60% EtOAc in hexanes to provide methyl 4'-{[(1R)-1-[(*tert*-butoxycarbonyl)amino]ethyl]-3-fluoro-1,1'-biphenyl-2-carboxylate (205 mg), found to be pure by LC/MS and proton NMR.

Methyl 4'-{(1R)-1-[(*tert*-butoxycarbonyl)amino]ethyl}-3-fluoro-1,1'-biphenyl-2-carboxylate (205 mg, 0.60 mmol) dissolved in MeOH (15 mL) was cooled to 0 °C. This homogenous solution was saturated with anhydrous hydrogen chloride and allowed to sit for 20 minutes. Dry nitrogen was then bubbled through the solution for about 30 minutes. Solvent was then removed under reduced pressure to yield an oily residue. The oil was then dissolved in DCM and the solvent removed. This process was repeated until a solid amine hydrochloride was obtained.

The above amine hydrochloride (85 mg, 0.27 mmol) along with 1-[(*tert*-butoxycarbonyl)amino]cyclopropanecarboxylic acid (55 mg, 0.27 mmol), HOBT•H₂O (8.4 mg, 0.05 mmol) and triethylamine (33 mg, 0.33 mmol) were dissolved in 4.5 mL of THF. To this room-temperature solution was added EDCI (74 mg, 0.38 mmol). After overnight stirring (*ca.* 16.5 h) the reaction mixture was diluted with water and EtOAc. The organic layer was washed successively with 1N HCl, 5% sodium bicarbonate, half-brine (x3) and then brine. The organic layer was dried over sodium sulfate, filtered and evaporated under reduced pressure to obtain a residue which was subjected to silica gel chromatography eluting with 1-6% MeOH in DCM. Collection of product containing fractions and removal of solvent yielded 108 mg (86%) of methyl 4'-{(1R)-1-[(1-[(*tert*-butoxycarbonyl)amino]cyclopropyl)carbonyl]-amino]ethyl}-3-fluoro-1,1'-biphenyl-2-carboxylate.

Methyl 4'-{(1R)-1-[(1-[(*tert*-butoxycarbonyl)amino]cyclopropyl)-carbonyl]amino]ethyl}-3-fluoro-1,1'-biphenyl-2-carboxylate (108 mg, 0.24 mmol) dissolved in MeOH (5.0 mL) was cooled to 0 °C. This homogenous solution was saturated with anhydrous hydrogen chloride and allowed to sit for 30 minutes. Dry nitrogen was then bubbled through the solution for about 50 min. Solvent was then removed under reduced pressure to yield an oily residue. The oil was then dissolved in DCM and the solvent removed. This process being repeated until a solid amine hydrochloride was obtained.

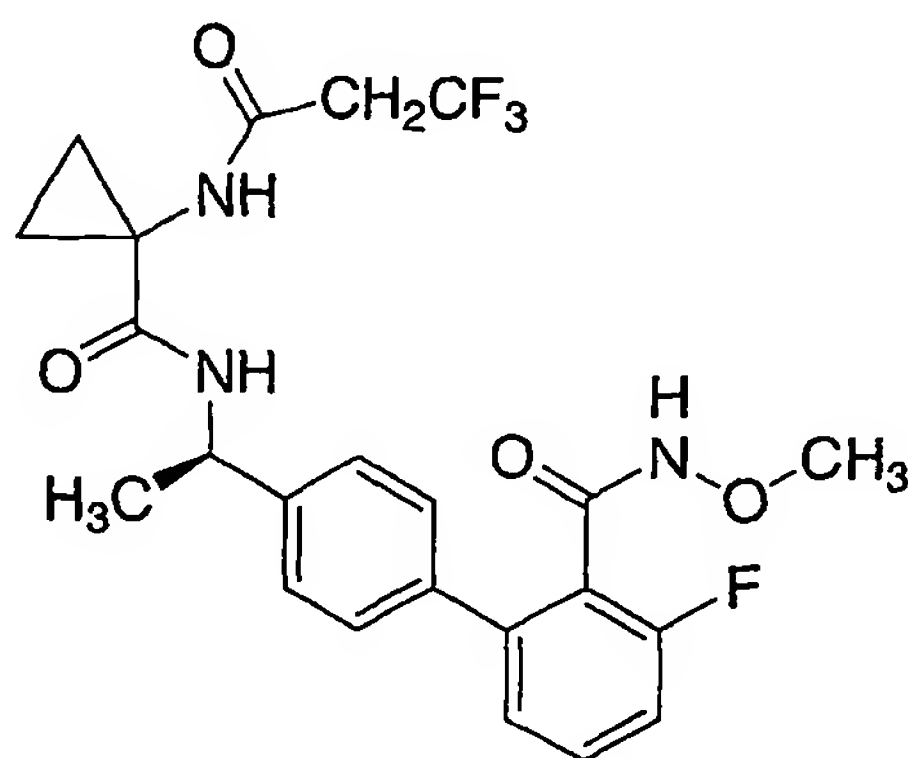
The above amine hydrochloride (46 mg, 0.12 mmol) along with trifluoropropionic acid (15 mg, 0.12 mmol), HOBT•H₂O (3.6 mg, 0.02 mmol) and triethylamine (14 mg, 0.14 mmol) were dissolved in 1.6 mL of THF plus 1.6 mL of DMF. To this room-temperature solution was added EDCI (31 mg, 0.16 mmol). After overnight stirring (*ca.* 18 h) the reaction mixture was diluted with water and EtOAc. The organic layer was washed successively with 1N HCl, 5% sodium bicarbonate, half-brine (x3) and then brine. The organic layer was dried over sodium sulfate, filtered and evaporated under reduced pressure to obtain a residue which was

subjected to silica gel chromatography eluting with 1-12% MeOH in DCM.

Collection of product containing fractions and removal of solvent yielded 36 mg (67%) of the title compound as a foaming solid. Purity was determined by LCMS (ES MS, $M+H^+$ found:467) and proton NMR (400 MHz, CD_3OD : δ 7.555, 7.540, 7.535, 7.520, 7.515, 7.500, 7.393, 7.373, 7.319, 7.302, 7.298, 7.240, 7.222, 7.221, 7.211, 7.188, 7.167, 7.165, 5.116, 5.099, 5.081, 5.064, 3.659, 3.268, 3.241, 3.214, 3.187, 1.508, 1.490, 1.483, 1.477, 1.474, 1.470, 1.465, 1.454, 1.444, 1.056, 1.049, 1.036, 1.031, 1.023, 1.007, 0.999, 0.995, 0.982, 0.974).

EXAMPLE 2

3-Fluoro-N-methoxy-4'-((1R)-1-[(1-[(3,3,3-trifluoropropanoyl)amino]cyclopropyl)-carbonyl]amino)ethyl)-1,1'-biphenyl-2-carboxamide



A solution of methyl 4'-((1R)-1-[(1-[(*tert*-butoxycarbonyl)amino]cyclopropyl)carbonyl]amino)ethyl)-3-fluoro-1,1'-biphenyl-2-carboxylate (466 mg, 1.0 mmol) in DCM (15 mL) and TFA (15 mL) was stirred under N_2 for 20 minutes at ambient temperature, then the organic solvent was removed under vacuum. The residue was dissolved in MeOH (20 mL), 4N NaOH (10 mL) and water (10 mL). This mixture was heated at reflux for 4 hours and then neutralized with 6N HCl. Purification was achieved by preparative HPLC on a delta-pack C_{18} column, 300 Å, pore size 15 μ M with 0.05% HCl acid -aqueous acetonitrile solvent systems using various linear gradients. Fractions containing product of 99% purity as measured by HPLC were combined and lyophilized to give 4'-((1R)-1-[(1-aminocyclopropyl)-carbonyl]amino)ethyl)-3-fluoro-1,1'-biphenyl-2-carboxylic acid as a white solid.

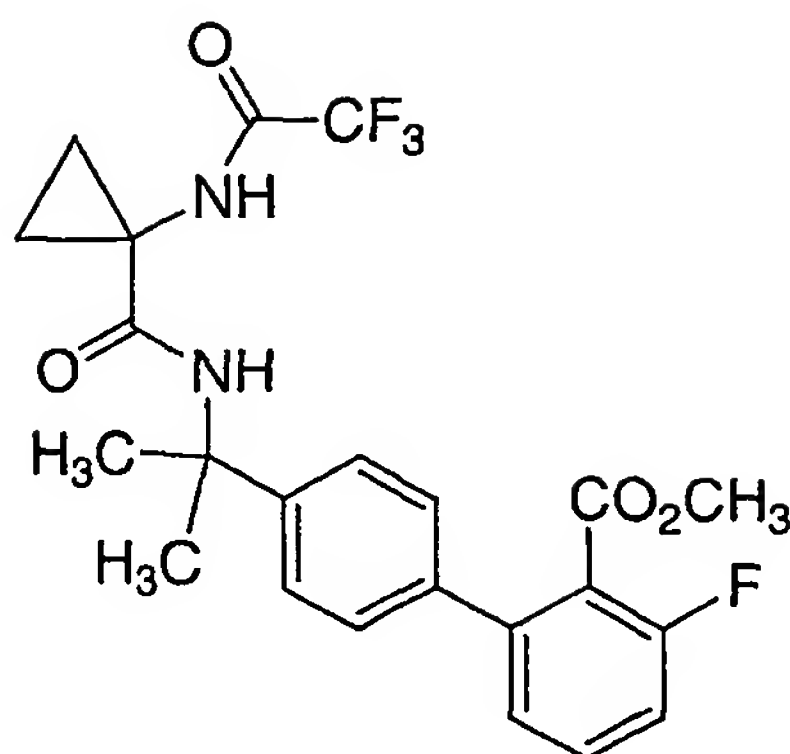
To a solution of trifluoropropionic acid (128 mg, 1.0 mmol) in DCM (1 mL), 1-ethyl-(3-dimethylaminopropyl)carbodiimide hydrochloride (229 mg, 1.2

mmol) and 1-hydroxy-7-azabenzotriazole (136 mg, 1.0 mmol) were added. The resulting solution was stirred at room temperature for 20 minutes, then 4'-((1R)-1-
5 {[(1-aminocyclopropyl)carbonyl]amino}ethyl)-3-fluoro-1,1'-biphenyl-2-carboxylic acid (171 mg, 0.5 mmol) in 1mL DCM was added, followed by *N,N*-diisopropylethyl-amine until pH = 10 was achieved. The reaction mixture was stirred at ambient temperature under N₂ for 2 hours, concentrated under vacuum and then partitioned between water and ethyl acetate. The organic extract was washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluted with 40%
10 MeOH in CHCl₃. Collection and concentration of appropriate fractions provided 3-fluoro-4'-{ (1R)-1-[(1-[(3,3,3-trifluoropropanoyl)amino]cyclopropyl)carbonyl]-amino]ethyl}-1,1'-biphenyl-2-carboxylic acid as a white powder.

To a solution of the above acid (226 mg, 0.50 mmol) in DCM (1 mL), 1-ethyl-(3-dimethylaminopropyl)carbodiimide hydrochloride (134 mg, 0.70 mmol), 1-
15 hydroxy-7-azabenzotriazole (68mg, 0.50 mmol) and methoxyamine hydrochloride (167 mg, 1.0 mmol) were added, followed by *N,N*-diisopropylethylamine until pH = 10 was achieved. The resulting solution was stirred at room temperature for 2 hours, and then partitioned between ethyl acetate and water. The organic extract was washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under
20 vacuum. Purification was achieved by preparative HPLC on a delta-pack C₁₈ column with 0.05% HCl acid -aqueous acetonitrile solvent systems using various linear gradients. Fractions containing product of 99% purity as measured by HPLC were combined and lyophilized to give the title compound as a white solid. . Purity was determined by LCMS (ES MS, M+H⁺ found:482) and proton NMR (400 MHz, DMSO-d₆) δ 1.40 (d, *J* = 7.1 Hz, 3H), 0.60-0.80 (m, 2H), 1.27 (m, 2H), 3.23 (m, *J* =
25 11.2 Hz, 2H). 3.44 (s, 3H), 5.02 (q, *J* = 8 Hz, 1H), 7.25-7.39 (m, 6H), 7.52 (m, 1H), 7.93 (d, *J* = 8.2Hz, 1H), 8.89 (s, 1H).

EXAMPLE 3

30 Methyl 3-fluoro-4'-{ 1-methyl-1-[(1-[(trifluoroacetyl)amino]cyclopropyl)-carbonyl]amino]ethyl}-1,1'-biphenyl-2-carboxylate



Methyl 2-(4-bromophenyl)-2-methylpropanoate (3.75 g, 14.6 mmol, prepared according to *J. Org. Chem.*, 59:2620-2622(1994)) in 150 mL of THF was allowed to react with potassium trimethylsilanolate (2.62 g, 20.4 mmol) at ambient temperature, for 60 hours, with continuous stirring. The reaction was then diluted with water and DCM. The pH of the aqueous phase was then adjusted to *ca.* 4, using 1M HCl. The aqueous layer was then extracted three times with additional DCM. The organic layers were pooled, dried over sodium sulfate, filtered and then concentrated to obtain 3.59 g of 2-(4-bromophenyl)-2-methylpropanoic acid, as a white solid, which gave LC/MS and proton NMR spectra consistent with theory.

To 82 mL of toluene was added the above acid (2.00 g, 8.23 mmol), triethylamine (1.20 mL, 8.64 mmol) and diphenylphosphoryl azide (1.86 mL, 8.64 mmol). After refluxing this mixture under nitrogen for 1 hour, benzyl alcohol (1.70 mL, 16.5 mmol) was added and the reaction mixture was allowed to reflux overnight. Solvent was removed under reduced pressure and the resulting oil was diluted with ethyl acetate. The ethyl acetate solution was washed twice with 5% sodium bicarbonate and once with brine. The organic layer was dried over sodium sulfate, filtered and evaporated under reduced pressure to obtain a residue which was subject to silica gel chromatography eluting with 0-2% MeOH in DCM. Collection of product containing fractions and removal of solvent yielded 2.26 grams of benzyl N-[1-(4-bromophenyl)-1-methylethyl]carbamate, which gave LC/MS and proton NMR spectra consistent with theory.

The above bromide (1.00 g, 2.87 mmol) was added to 25 mL of DMF, followed by bis(pinacolato)boron (0.875 g, 3.45 mmol), potassium acetate (0.846 g, 8.62 mmol) and PdCl₂(dppf)2•CH₂Cl₂ (.063 g, 0.090 mmol). This mixture was heated to 80 °C, under nitrogen, for 3 hours. After cooling to ambient temperature, methyl 2-fluoro-6-iodobenzoate (0.965 g, 3.45 mmol), PdCl₂(dppf)2•CH₂Cl₂ (.063 g,

0.090 mmol) and aqueous sodium carbonate (7.18 mL, 2M, 14.4 mmol) were added. This mixture was then heated to 80 °C overnight. After cooling to ambient temperature, most of the DMF was removed under reduced pressure and the biphasic mixture was diluted with ethyl acetate. The pH of the aqueous layer was made neutral
5 with 1M HCl, prior to extraction with two additional volumes of ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and evaporated under reduced pressure to obtain a residue which was subject to silica gel chromatography eluting with 0-2% MeOH in DCM. Collection of product containing fractions and removal of solvent yielded 0.25 grams of methyl 4'-(1-
10 {[(benzyloxy)carbonyl]amino}-1-methylethyl)-3-fluoro-1,1'-biphenyl-2-carboxylate, which gave LC/MS and proton NMR spectra consistent with theory.

Methyl 4'-(1-{[(benzyloxy)carbonyl]amino}-1-methylethyl)-3-fluoro-1,1'-biphenyl-2-carboxylate (0.25 g, 0.59 mmol) was dissolved in 6.0 mL of anhydrous ethanol. Pd/C (90 mg) was then added and the nitrogen atmosphere was
15 exchanged for hydrogen. The reaction mixture was allowed to stir for 72 hours. After filtration through celite, the ethanol was removed under reduced pressure to yield 0.15 grams of methyl 4'-(1-amino-1-methylethyl)-3-fluoro-1,1'-biphenyl-2-carboxylate which was of sufficient purity to use directly in the next reaction.

The above-mentioned amine (80 mg, 0.28 mmol), was dissolved in
20 anhydrous DCM (4 mL). To this stirred solution was added 1-[(*tert*-butoxycarbonyl)-amino]cyclopropanecarboxylic acid (67 mg, 0.33 mmol), HOBt•H₂O (8 mg, 0.08 mmol) and lastly EDCI (69 g, 0.36 mmol). This mixture was allowed to stir overnight. Solvent was then removed under reduced pressure and the residue was subjected to silica gel chromatography eluting with a 1-3% MeOH in DCM gradient
25 to provide methyl 4'-{1-[(1-[(*tert*-butoxycarbonyl)amino]cyclopropyl)carbonyl)-amino]-1-methylethyl}-3-fluoro-1,1'-biphenyl-2-carboxylate (82 mg), giving LC/MS and proton NMR spectra consistent with theory.

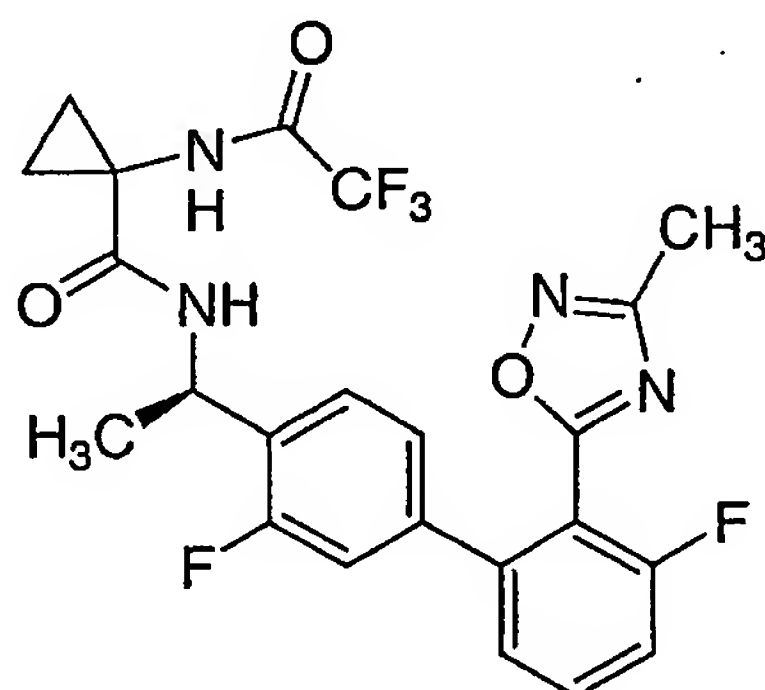
The above material (82 mg, 0.17 mmol) dissolved in ethyl acetate (4 mL) was cooled to 0 °C. This homogenous solution was saturated with anhydrous
30 hydrogen chloride and allowed to sit for 30 minutes. Dry nitrogen was then bubbled through the solution for about 30 minutes. Solvent was then removed under reduced pressure to yield an oily residue, which was used directly in the next reaction.

To a 0 °C, stirred solution of the above mentioned amine (32 mg, 0.09 mmol) in DCM (2.0 mL) was added triethylamine (20 µL, 0.13 mmol) and lastly
35 trifluoroacetic anhydride (20 µL, 0.11 mmol). After 10 minutes the ice bath was

remove and stirring was continued for a total of 30 minutes. The reaction mixture was subject to silica gel chromatography eluting with 0.5-2% MeOH in DCM. Collection of product containing fractions and removal of solvent yielded 34 mg (84%) of the title compound as a foaming solid. Purity was determined by LCMS (ES MS, $M + H^+$ found: 467) and proton NMR (400 MHz, CD_3OD : δ 7.552, 7.537, 7.531, 7.517, 7.512, 7.497, 7.442, 7.425, 7.420, 7.302, 7.297, 7.280, 7.250, 7.231, 7.203, 7.181, 7.159, 3.644, 1.664, 1.444, 1.432, 1.424, 1.412, 1.080, 1.068, 1.060, 1.048).

EXAMPLE 4

10 N-((1R)-1-[3,3'-difluoro-2'-(3-methyl-1,2,4-oxadiazol-5-yl)-1,1'-biphenyl-4-yl]ethyl)-1-[(trifluoroacetyl)amino]cyclopropanecarboxamide



15 To a solution of 2-fluoro-6-iodobenzoic acid (15.00g, 56.39 mmol) in 150 mL CH_2Cl_2 containing 0.1 mL DMF was added oxalyl chloride (9.30g, 73.3 mmol) dropwise. The solution was stirred at room temperature for 75 minutes, then concentrated in vacuo. The residue was re-dissolved in 150 mL CH_2Cl_2 , and the solution was saturated three times with ammonia gas. The solution was concentrated

20 in vacuo and dried under vacuum overnight. The residue was dissolved in N,N-dimethylacetamide dimethyl acetal (24.7 mL, 0.169 mol) and heated to 120 °C for 5 hours. Additional N,N-dimethylacetamide dimethyl acetal (25 mL, 0.17 mol) was added over the course of the reaction to drive it to completion. The solution was cooled to room temperature, concentrated in vacuo, and dried under vacuum

25 overnight. To a solution of the intermediate in 57 mL dioxane was added hydroxylamine hydrochloride (4.704g, 67.69 mmol), 5N NaOH (13.5 mL, 67.7 mmol), and 70% acetic acid (57 mL). The mixture was stirred at 60 °C for 2 hours, then at 90 °C for 3 hours. The resulting solution was cooled to room temperature,

diluted with ethyl acetate, and neutralized with aqueous sodium bicarbonate. The organic extract was washed with aqueous sodium bicarbonate and brine, dried over sodium sulfate, filtered and concentrated under vacuum. The residue was filtered through silica gel eluted with 10% ethyl acetate in hexanes to provide 5-(2-fluoro-6-iodophenyl)-3-methyl-1,2,4-oxadiazole as orange yellow crystals that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 305.06 for M+H⁺.

To a solution of (S)-(-)-2-methyl-2-propanesulfinamide (20.20 g, 0.167 mol) in 350 mL CH₂Cl₂ were added 4-bromo-2-fluorobenzaldehyde (35.53g, 0.1750 mol), pyridinium-p-toluenesulfonate (2.09g, 8.33 mmol), and magnesium sulfate (200.6 g, 1.667 mol). The reaction mixture was stirred at room temperature for 48 hours. Additional magnesium sulfate (100.3g, 0.833 mol) was added, and the reaction was stirred 24 hours. The mixture was filtered through celite, washing with CH₂Cl₂ and concentrated in vacuo. The resulting residue was subjected to column chromatography on silica gel eluted with 0-10% ethyl acetate in hexanes to afford N-[(1E)-(4-bromo-2-fluorophenyl)methylidene]-2-methylpropane-2-sulfinamide as a white solid that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 308.09 for M+H⁺(⁸¹Br).

To a solution of N-[(1E)-(4-bromo-2-fluorophenyl)methylidene]-2-methylpropane-2-sulfinamide (32.65g, 0.1066 mol) in 550 mL CH₂Cl₂ at -48 °C was added methylmagnesium chloride (3.0 M solution in ether, 53.31 mL, 0.1599 mol) dropwise. The reaction was quenched with aqueous ammonium chloride and the aqueous layer was extracted with methylene chloride. The combined organics were dried over Na₂SO₄, filtered and concentrated under vacuum. The resulting residue was subjected to column chromatography on silica gel eluted with 10-50% ethyl acetate in hexanes to afford N-[(1R)-1-(4-bromo-2-fluorophenyl)ethyl]-2-methylpropane-2-sulfinamide as a white solid that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 324.14 for M+H⁺(⁸¹Br).

To a solution of N-[(1R)-1-(4-bromo-2-fluorophenyl)ethyl]-2-methylpropane-2-sulfinamide (26.29g, 81.58 mmol) in 40 mL methanol was added HCl/dioxane (4M, 40.8 mL, 0.163 mol) solution. The reaction mixture was concentrated in vacuo, and ether was added. The white solid was collected, washing with cold ether, and dried under vacuum to yield (1R)-1-(4-bromo-2-fluorophenyl)ethanaminium chloride that gave proton NMR spectra consistent with theory.

To a solution of the above (1R)-1-(4-bromo-2-fluorophenyl)-ethanaminium chloride (14.24g, 55.95 mmol) in 300 mL CH₂Cl₂ at 0 °C was added di-tert-

butyl dicarbonate (17.98g, 82.40 mmol) and triethylamine (8.256 g, 81.58 mmol). The solution was washed with water and brine, dried over Na₂SO₄, filtered and concentrated under vacuum to provide crude (1R)-1-(4-bromo-2-fluorophenyl)ethanaminium chloride as a white solid that gave proton NMR spectra consistent with theory.

A mixture of (1R)-1-(4-bromo-2-fluorophenyl)ethanaminium chloride (26.42g, 83.03 mmol), bis(pinacolato)diboron (31.63g, 0.1246 mol), potassium acetate (24.45 g, 0.2491 mol), and [1,1'-bis(diphenylphosphino)ferrocene]-palladium(II) dichloride (0.265 g, 0.362 mmol) in 80 mL DMSO was heated to 90 °C under N₂ for 3 hours. The mixture was then cooled to room temperature and partitioned between ethyl acetate and water. The organic extract was washed with water and brine, dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was subjected to silica gel chromatography eluted with 0-10% ethyl acetate in hexanes to provide tert-butyl (1R)-1-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethylcarbonate as a beige solid that gave proton NMR spectra consistent with theory.

A mixture of 5-(2-fluoro-6-iodophenyl)-3-methyl-1,2,4-oxadiazole (1.50g, 4.93 mmol), tert-butyl (1R)-1-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethylcarbonate (1.80 g, 4.93 mmol), potassium carbonate (1.70 g, 12.3 mmol), tri-*o*-tolylphosphine (0.060 g, 0.20 mmol), and palladium acetate (0.011 g, 0.05 mmol) in 25 mL of THF and 4 mL of water was heated in a sealed flask at 100°C overnight. The mixture was then cooled and concentrated in vacuo. The resulting residue was dissolved in ethyl acetate, washed with water and brine, dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was subjected to silica gel chromatography eluted with 0-10% ethyl acetate and hexane to provide tert-butyl (1R)-1-[3,3'-difluoro-2'-(3-methyl-1,2,4-oxadiazol-5-yl)-1,1'-biphenyl-4-yl]-ethylcarbamate as a yellow oil that gave proton NMR spectra consistent with theory. The product was dissolved in ethyl acetate and saturated with HCl gas. The solution was concentrated in vacuo and azeotroped 3 times with toluene to provide (1R)-1-[3,3'-difluoro-2'-(3-methyl-1,2,4-oxadiazol-5-yl)-1,1'-biphenyl-4-yl]ethanaminium chloride.

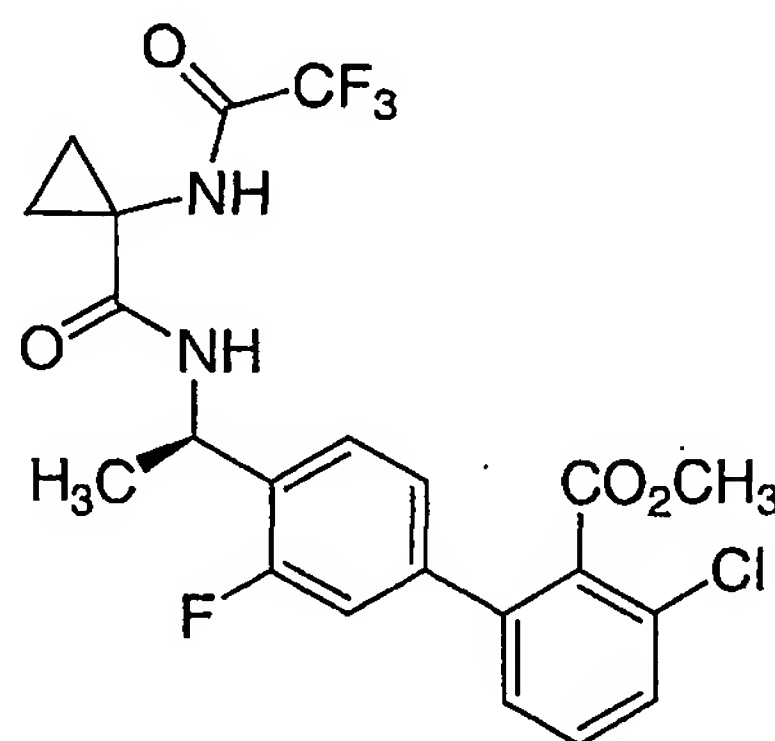
A solution of (1R)-1-[3,3'-difluoro-2'-(3-methyl-1,2,4-oxadiazol-5-yl)-1,1'-biphenyl-4-yl]ethanaminium chloride (0.500g, 1.42 mmol), Boc-1-aminocyclopropane-1-carboxylic acid (0.300g, 1.49 mmol), 1-ethyl-(3-dimethylaminopropyl)-carbodiimide hydrochloride (0.545 g, 2.84 mmol), 1-hydroxy-7-azabenzotriazole

(0.010 g, 0.15 mmol), and triethylamine (0.863 g, 8.53 mmol) in 10 mL CH₂Cl₂ was stirred at room temperature overnight. The solution was washed with aqueous sodium bicarbonate and brine, dried over Na₂SO₄, filtered and concentrated. The residue was subjected to silica gel chromatography eluted with 10-40% ethyl acetate in hexanes to provide tert-butyl 1-[(1R)-1-[3,3'-difluoro-2'-(3-methyl-1,2,4-oxadiazol-5-yl)-1,1'-biphenyl-4-yl]ethyl]amino)carbonyl]cyclopropylcarbamate as a white solid that gave proton NMR spectra consistent with theory. The product was dissolved in ethyl acetate and saturated with HCl gas. The solution was concentrated in vacuo and azeotroped 3 times with toluene to provide 1-[(1R)-1-[3,3'-difluoro-2'-(3-methyl-1,2,4-oxadiazol-5-yl)-1,1'-biphenyl-4-yl]ethyl]amino)carbonyl]-cyclopropanaminium chloride that gave a mass ion (ES⁺) of 399.21 for M+H⁺.

To a solution of the above compound (0.290 g, 0.667 mmol) in 5 mL CH₂Cl₂ at 0 °C was added triethylamine (0.135 g, 1.33 mmol) and trifluoroacetic anhydride (0.14 g, 0.67 mmol). The solution was diluted with addition CH₂Cl₂ and washed with aqueous sodium bicarbonate and brine, dried over Na₂SO₄, filtered and concentrated. The residue was subjected to silica gel chromatography eluted with 10-40% ethyl acetate in hexanes to provide the title compound that gave proton NMR spectra consistent with theory and a mass ion (ES⁺) of 495.22 for M+H⁺: ¹H NMR (300 MHz, MeOH-d₄) δ 9.71 (s, 1H), 8.29 (d, *J* = 8.3 Hz, 1H), 7.77-7.70 (m, 1H), 7.41-7.30 (m, 3H), 6.95 (s, 1H), 6.93-6.91 (m, 1H), 5.32-5.22 (m, 1H), 2.36 (s, 3H), 1.51-1.45 (m, 5H), 1.15-1.01 (m, 2H).

EXAMPLE 5

Methyl 3-chloro-3'-fluoro-4'--[(1R)-1-[(1-[(trifluoroacetyl)amino]cyclopropyl)-carbonyl]amino]ethyl}-1,1'-biphenyl-2-carboxylate



To a solution of n-BuLi (2.5M in hexanes, 41.8mL, 0.104 mol) in 400 mL THF at -78 °C was added 2,2,6,6-tetramethylpiperidine (14.76 g, 0.1045 mol) dropwise followed by 3-bromochlorobenzene (20.00g, 0.1045 mol) dropwise. The mixture was stirred at -78 °C for 2h, then quenched with dry ice and warmed to room temperature. The solution was concentrated in vacuo and the resulting residue was dissolved in water and washed with ether. To the aqueous fraction was added 1N HCl to pH = 2, and the product was extracted with CH₂Cl₂. The combined organics were dried over Na₂SO₄, filtered and concentrated under vacuum to provide 2-bromo-6-chlorobenzoic acid that gave proton NMR spectra consistent with theory.

To a solution of 2-bromo-6-chlorobenzoic acid (17.7g, 75.2 mmol) in methanol (200 mL) at 0 °C was added (trimethylsilyl)diazomethane (2M in hexanes, 100 mL, 0.200 mol). The solution was stirred at 0 °C for 1.5 hours, then warmed to room temperature and washed with aqueous sodium bicarbonate and brine, dried over Na₂SO₄, filtered and concentrated. The residue was subjected to silica gel chromatography eluted with 0-5% ethyl acetate in hexanes to provide methyl 2-bromo-6-chlorobenzoate as a pale yellow oil that gave proton NMR spectra consistent with theory.

A mixture of methyl 2-bromo-6-chlorobenzoate (2.25g, 9.03 mmol), tert-butyl (1R)-1-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-ethylcarbonate (see Example 11, 3.00 g, 8.21 mmol), potassium carbonate (2.84 g, 20.5 mmol), tri-o-tolylphosphine (0.10 g, 0.33 mmol), and palladium acetate (0.018 g, 0.08 mmol) in 40 mL of THF and 4 mL of water was heated in a sealed flask at 100°C for 4h. The mixture was then cooled and concentrated in vacuo. The resulting residue was dissolved in ethyl acetate, washed with water and brine, dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was subjected to silica gel chromatography eluted with 0-10% ethyl acetate and hexane to provide methyl 4'-{(1R)-1-[(tert-butoxycarbonyl)amino]ethyl}-3-chloro-3'-fluoro-1,1'-biphenyl-2-carboxylate that gave proton NMR spectra consistent with theory. The product was dissolved in ethyl acetate and saturated with HCl gas. The solution was concentrated in vacuo and azeotroped 3x with toluene to provide (1R)-1-[3'-chloro-3-fluoro-2'-(methoxycarbonyl)-1,1'-biphenyl-4-yl]ethanaminium chloride.

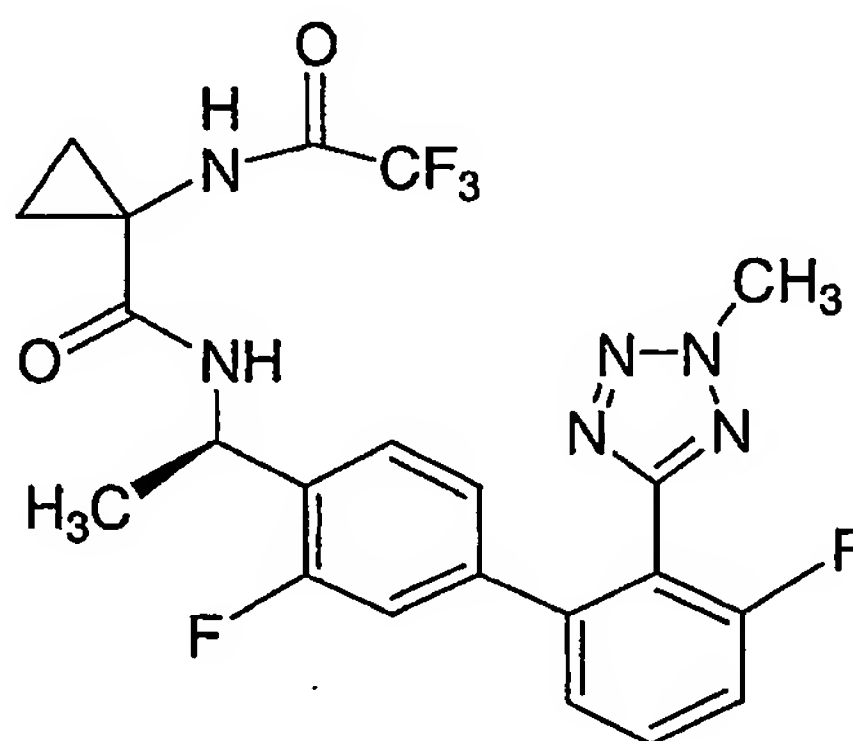
A solution of the above compound (1.00g, 2.91 mmol), boc-1-amino-cyclopropane-1-carboxylic acid (0.614g, 3.05 mmol), 1-ethyl-(3-dimethylamino-propyl)carbodiimide hydrochloride (1.11g, 5.81 mmol), 1-hydroxy-7-azabenzotriazole (0.010 g, 0.15 mmol), and triethylamine (1.76 g, 17.4 mmol) in 20 mL CH₂Cl₂ was

stirred at room temperature overnight. The solution was washed with aqueous sodium bicarbonate and brine, dried over Na₂SO₄, filtered and concentrated. The residue was subjected to silica gel chromatography eluted with 10-40% ethyl acetate in hexanes to provide methyl 4'-{(1R)-1-[(1-[(tert-butoxycarbonyl)amino]cyclopropyl)carbonyl]-amino]ethyl}-3-chloro-3'-fluoro-1,1'-biphenyl-2-carboxylate as a white solid that gave proton NMR spectra consistent with theory. The product was dissolved in ethyl acetate and saturated with HCl gas. The solution was concentrated in vacuo and azeotroped three times with toluene to provide 1-[(1R)-1-[3'-chloro-3-fluoro-2'-(methoxycarbonyl)-1,1'-biphenyl-4-yl]ethyl]amino)carbonyl]cyclopropanaminium chloride that gave a mass ion (ES+) of 391.21 for M+H⁺.

To a solution of the above compound (0.300 g, 0.702 mmol) in 5 mL CH₂Cl₂ at 0 °C was added triethylamine (0.142 g, 1.40 mmol) and trifluoroacetic anhydride (0.147 g, 0.70 mmol). The solution was diluted with addition CH₂Cl₂ and washed with aqueous sodium bicarbonate and brine, dried over Na₂SO₄, filtered and concentrated. The residue was subjected to silica gel chromatography eluted with 10-40% ethyl acetate in hexanes to provide the title compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 487.22 for M+H⁺: ¹H NMR (300 MHz, MeOH-d₄) δ 7.51-7.33 (m, 4H), 7.17-7.07 (m, 2H), 5.31 (q, J = 7.1 Hz, 1H), 3.69 (s, 3H), 1.52-1.49 (m, 5H), 1.27-1.03 (m, 2H).

EXAMPLE 6

N-{(1R)-1-[3,3'-difluoro-2'-(2-methyl-2H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]ethyl}-1-[(trifluoroacetyl)amino]cyclopropanecarboxamide



A solution of 2-fluoro-6-iodobenzonitrile (17.82g, 72.15 mmol) and azidotrimethyltin (15.00g, 72.88 mmol) in 150 mL toluene was heated to 125 °C for 72 hours. The solution was cooled to room temperature and partitioned between ethyl acetate and 0.5 N HCl. The organic extract was washed with water and brine, dried
5 over Na₂SO₄, filtered and concentrated under vacuum to provide 5-(2-fluoro-6-iodophenyl)-1H-tetrazole that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 291.01 for M+H⁺.

A mixture of 5-(2-fluoro-6-iodophenyl)-1H-tetrazole (23.48g, 80.97 mmol), potassium carbonate (16.79g, 0.121 mol), and iodomethane (16.09g, 0.113
10 mol) in 25 mL DMF was stirred at room temperature for 3 hours. The mixture was partitioned between ethyl acetate and water, and the organic extract was washed with water and brine, dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was subjected to silica gel chromatography eluted with 0-10% ethyl acetate in hexanes to provide 5-(2-fluoro-6-iodophenyl)-2-methyl-2H-tetrazole that gave proton
15 NMR spectra consistent with theory and a mass ion (ES+) of 305.06 for M+H⁺.

To a solution of 2-fluoro-4-bromo-benzaldehyde (20.0 g, 98.5 mmol) in 500 mL of THF at 0 °C was added slowly a solution methyllithium (1.4 M in Et₂O, 70.3 mL). After one hour the reaction was carefully quenched with saturated aqueous ammonium chloride, extracted with diethyl ether, washed with saturated NaCl, dried
20 over MgSO₄, and concentrated. A solution of the crude alcohol in 200 mL of CH₂Cl₂ and TEA (14.0 mL, 100 mmol) at 0 °C was added methanesulfonyl chloride (7.42 mL, 95.9 mmol) over a period of five minutes. After and overnight reaction period, the reaction was extracted with CH₂Cl₂, washed with NaHCO₃, saturated NaCl, dried over MgSO₄, and concentrated. A solution of the crude mesylate in 50
25 mL of DMF was treated with sodium azide (12.5 g, 191 mmol) overnight. The reaction was extracted with EtOAc, washed with NaHCO₃, saturated NaCl, dried over MgSO₄, and concentrated. To a solution of the crude azide in 100 mL of THF was triethylphosphine (1 M in THF, 90.1 mL) over a period of 30 minutes. After one hour, 100 mL of 1 N HCl was added and the mixture was heated overnight. The
30 mixture was cooled and washed with Et₂O. The aqueous layer was made basic by the addition of potassium carbonate, extracted with Et₂O, dried over MgSO₄, and concentrated. A solution of the crude amine (9.0 g, 41.2 mmol) in 50 mL of CH₂Cl₂ was treated with Boc anhydride (9.00 g, 41.2 mmol). After one hour the mixture was concentrated. A solution of the crude carbamate in 40 mL of DMSO was added
35 potassium acetate (12.1 g, 123.1 mmol), bis(pinacolato)diboron (11.5 g, 45.4 mmol),

and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (1.4 g, 1.8 mmol). The resulting mixture was heated at 80 °C for 16 hours. After cooling to room temperature, the mixture was partitioned between water and EtOAc. The organic extract was washed with brine, dried over MgSO₄, filtered and concentrated under vacuum. The residue was subjected to silica gel chromatography eluted with 20% ethyl acetate in hexanes to provide tert-butyl 1-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethylcarbamate as a tacky solid that gave a proton NMR consistent with theory.

5 A mixture of 5-(2-fluoro-6-iodophenyl)-2-methyl-2H-tetrazole (1.49g, 4.89 mmol), tert-butyl 1-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethylcarbamate (1.70g, 4.65 mmol), potassium carbonate (1.61 g, 11.6 mmol), tri-*o*-tolylphosphine (0.057 g, 0.19 mmol), and palladium acetate (0.010 g, 0.05 mmol) in 20 mL of THF and 4 mL of water was heated in a sealed flask at 100 °C overnight. The mixture was then cooled and concentrated in vacuo. The resulting residue was dissolved in ethyl acetate, washed with water and brine, dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was subjected to silica gel chromatography eluted with 0-20% ethyl acetate and hexane to provide tert-butyl 1-[3,3'-difluoro-2'-(2-methyl-2H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]ethylcarbamate as a yellow oil that gave proton NMR spectra consistent with theory. The product was dissolved in ethyl acetate and saturated with HCl gas. The solution was concentrated in vacuo and azeotroped 3x with toluene to provide 1-[3,3'-difluoro-2'-(2-methyl-2H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]ethanaminium chloride.

15 A solution of 1-[3,3'-difluoro-2'-(2-methyl-2H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]ethanaminium chloride (0.670g, 1.89 mmol), Boc-1-aminocyclopropane-1-carboxylic acid (0.419g, 2.08 mmol), 1-ethyl-(3-dimethylaminopropyl)-carbodiimide carboxylic acid (0.726g, 3.79 mmol), 1-hydroxy-7-azabenzotriazole (0.010g, 0.15 mmol), and triethylamine (1.15g, 11.4 mmol) in 10 mL CH₂Cl₂ was stirred at room temperature for 48 hours. The solution was washed with aqueous sodium bicarbonate and brine, dried over Na₂SO₄, filtered and concentrated. The residue was subjected to silica gel chromatography eluted with 10-50% ethyl acetate in hexanes to provide tert-butyl 1-[(1-[3,3'-difluoro-2'-(2-methyl-2H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]ethyl)amino]carbonylcyclopropylcarbamate that gave proton NMR spectra consistent with theory and a mass ion (ES⁺) of 499.7 for M+H⁺. The enantiomers were resolved at this point on a Chiralcel OD column 10% isopropanol/

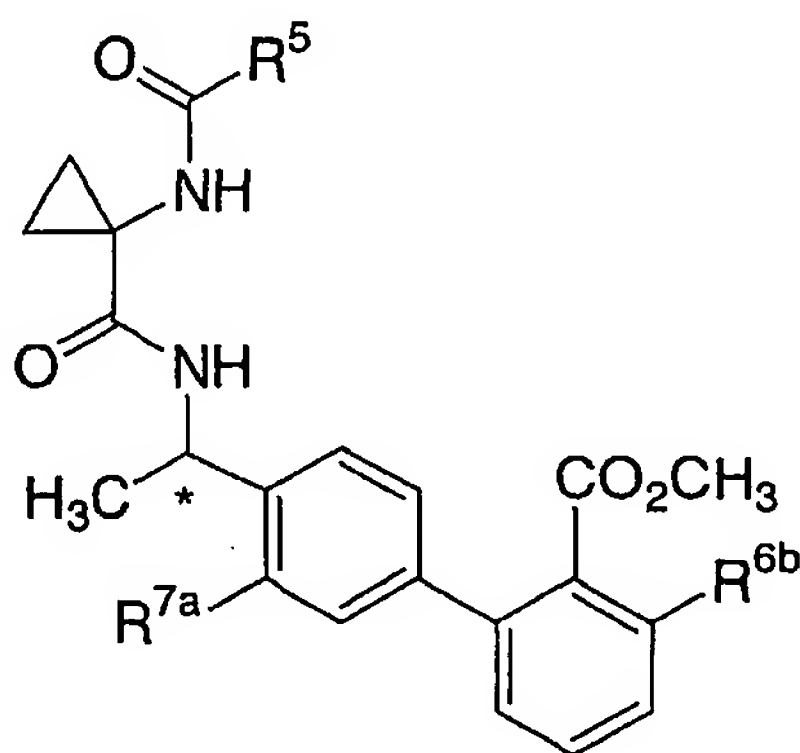
hexane (containing 0.1% TFA). The R enantiomer eluted first and was used for the remainder of the synthesis.

The above product was dissolved in ethyl acetate and saturated with HCl gas. The solution was concentrated in vacuo and azeotroped 3x with toluene to provide (1R) 1-[(1-[3,3'-difluoro-2'-(2-methyl-2H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]-ethyl)amino)carbonyl]cyclopropanaminium chloride that gave a mass ion (ES+) of 399.6 for M+H⁺.

To a solution of the above compound (0.105g, 0.241 mmol) in 2 mL CH₂Cl₂ at 0 °C was added triethylamine (0.049g, 0.48 mmol) and trifluoroacetic anhydride (0.051g, 0.24 mmol). The solution was diluted with additional CH₂Cl₂ and washed with aqueous sodium bicarbonate and brine, dried over Na₂SO₄, filtered and concentrated. The residue was subjected to silica gel chromatography eluted with 10-40% ethyl acetate in hexanes to provide the title compound that gave proton NMR spectra consistent with theory and a mass ion (ES+) of 495.32 for M+H⁺: ¹H NMR (300 MHz, MeOH-d₄) δ 7.68-7.61 (m, 1H), 7.34-7.21 (m, 3H), 6.89-6.83 (m, 2H), 5.23 (d, *J* = 7.1 Hz, 1H), 4.86 (s, 3H), 1.49 (d, *J* = 3.7 Hz, 2H), 1.44 (d, *J* = 7.1 Hz, 3H), 1.18-1.01 (m, 2H).

The following compounds in Table 1 were prepared by methods
20 analogous to those described in Example 1.

Table 1



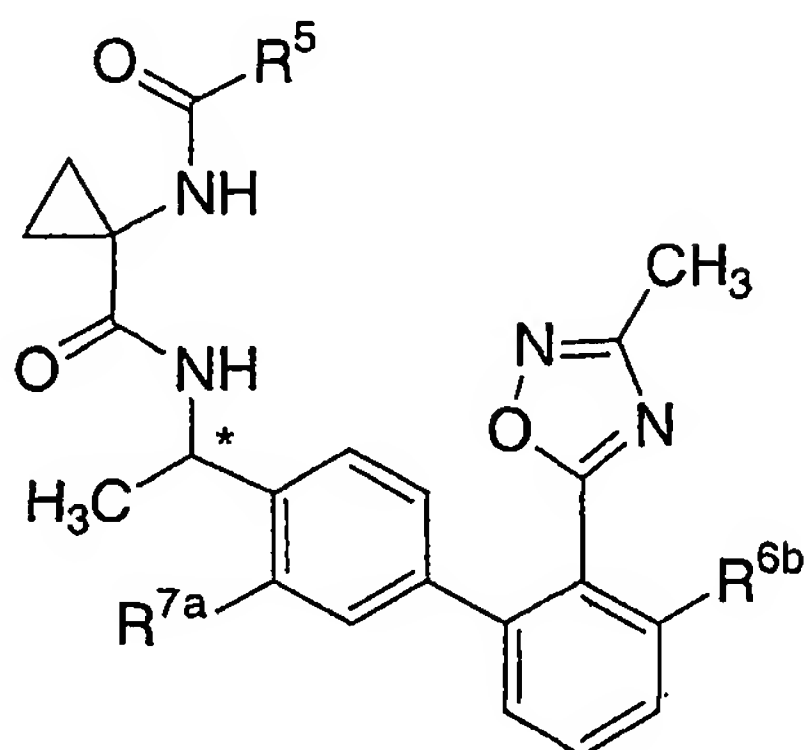
Example	R5	R6b	R7a	*	ES MS, M+H ⁺
7	cyanomethyl	F	H	R	424
8	cyanomethyl	Cl	H	R	440
9	2,2,2-trifluoroethyl	Cl	H	R	482
10	2,2,2-trifluoroethyl	F	F	(±)	485
11	isoxazol-5-yl	F	F	(±)	470
12	cyanomethyl	F	F	(±)	442
13	pyrimidin-5-yl	F	H	R	463
14	2,2,2-trifluoroethyl	F	F	S	485
15	2,2,2-trifluoroethyl	F	F	R	485
16	pyrimidin-5-yl	F	F	(±)	481
17	isoxazol-5-yl	F	F	R	470
18	trifluoromethyl	F	F	R	471
19	pyrimidin-5-yl	F	F	R	481
20	isoxazol-5-yl	F	F	S	470
21	trifluoromethyl	F	F	S	471
22	pyrimidin-5-yl	F	F	S	481
23	methyl	F	F	R	417
24	5-bromopyridin-3-yl	F	F	R	558
25	5-bromo-1-oxido- pyridin-3-yl	F	F	R	574
26	trifluoromethyl	H	F	R	453
27	pyrimidin-5-yl	H	F	R	463
28	chlorodifluoromethyl	F	F	R	487
29	5-(trifluoromethyl)- pyridin-3-yl	F	F	R	548
30	chlorodifluoromethyl	Cl	F	R	503
31	difluoromethyl	F	F	R	453
32	pentafluoroethyl	F	F	R	521
33	difluoromethyl	Cl	F	R	469

* stereoconfiguration at designated chiral center; (±) = racemic mixture

The following compounds in Table 2 were prepared by methods analogous to those described in Example 1.

Table 2

5



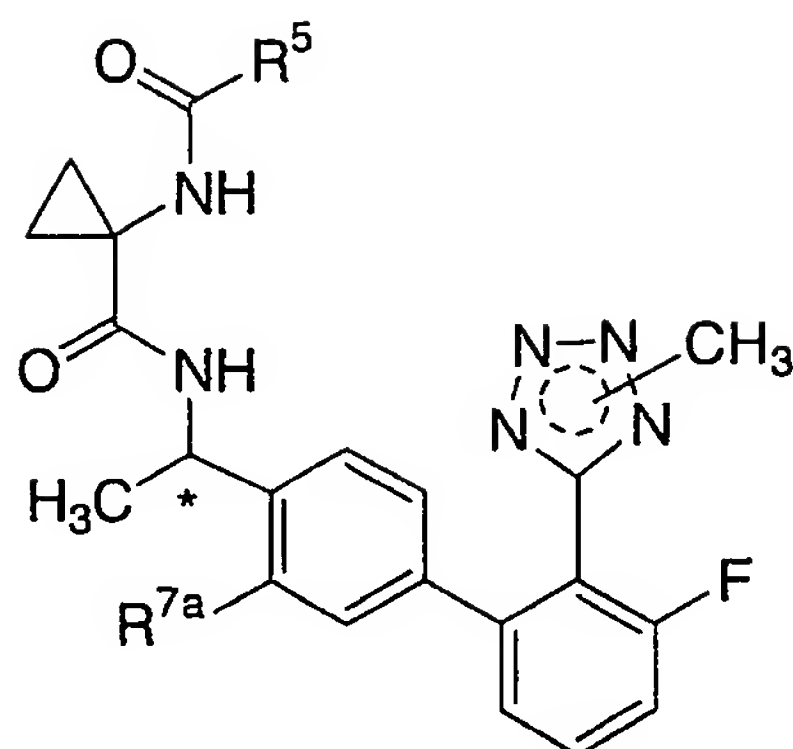
Example	R5	R6b	R7a	*	ES MS, M+H ⁺
34	methyl	F	H	R	423
35	cyanomethyl	F	H	R	448
36	2,2,2-trifluoroethyl	F	H	R	491
37	isoxazol-5-yl	F	H	R	476
38	2,2,2-trifluoroethyl	F	F	S	509
39	2,2,2-trifluoroethyl	F	F	R	509
40	cyanomethyl	F	F	(±)	466
41	2,2,2-trifluoroethyl	F	F	(±)	509
42	pyrimidin-5-yl	F	F	(±)	505
43	chloro(difluoro)methyl	F	F	R	511
44	pyrimidin-5-yl	F	F	R	505
45	difluoromethyl	F	F	R	477

* stereoconfiguration at designated chiral center; (±) = racemic mixture

10

The following compounds in Table 3 were prepared by methods analogous to those described in Example 1.

Table 3



5

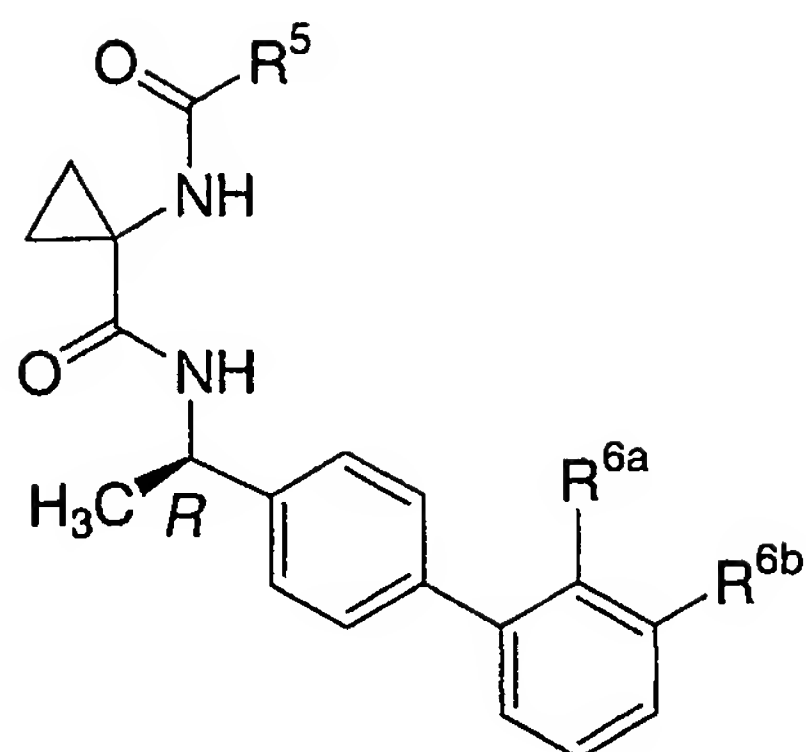
Example	R ⁵	R ^{7a}	tetrazole	*	ES MS, M+H ⁺
46	cyanomethyl	H	2H	R	448
47	2,2,2-trifluoroethyl	H	2H	R	491
48	cyanomethyl	H	1H	R	448
49	2,2,2-trifluoroethyl	H	1H	R	491
50	methyl	H	1H	R	423
51	isoxazol-5-yl	F	2H	(±)	494
52	2,2,2-trifluoroethyl	F	2H	(±)	509
53	pyrimidin-5-yl	F	2H	(±)	505
54	trifluoromethyl	F	2H	S	495
55	chloro(difluoro)methyl	F	2H	R	511
56	difluoromethyl	F	2H	R	477

* stereoconfiguration at designated chiral center; (±) = racemic mixture

The following compounds in Table 4 were prepared by methods analogous to those described in Example 1.

10

Table 4



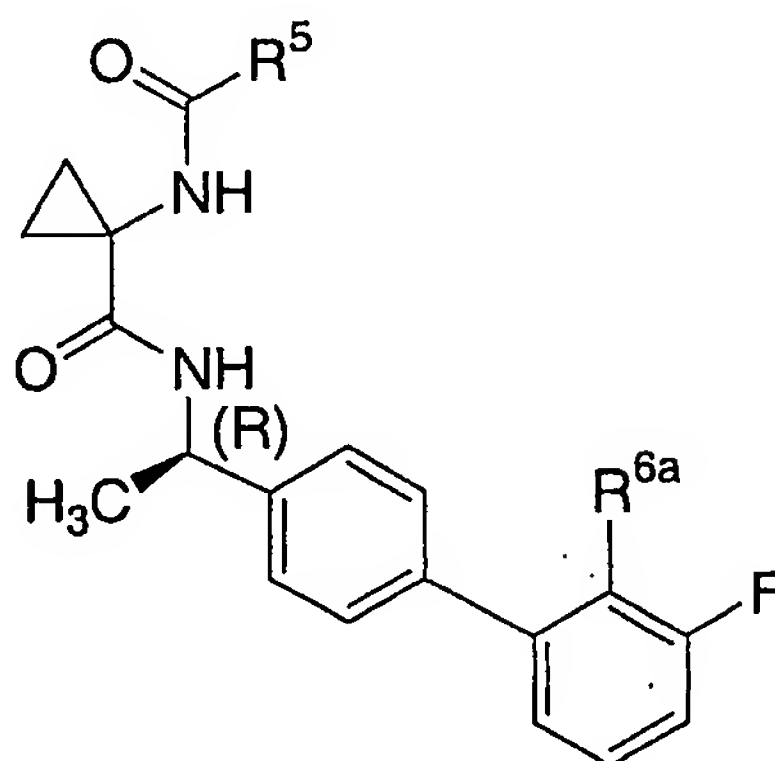
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Example	R ⁵	R ^{6a}	R ^{6b}	ES MS, M+H ⁺
57	2,2,2-trifluoroethyl	cyano	F	434
58	2,2,2-trifluoroethyl	difluoromethoxy	H	457
59	2,2,2-trifluoroethyl	trifluoromethoxy	H	475
60	2,2,2-trifluoroethyl	trifluoromethyl	F	478
61	2,2,2-trifluoroethyl	Cl	Cl	459
62	isoxazol-5-yl	trifluoromethyl	F	462
63	cyanomethyl	trifluoromethyl	F	434
64	isoxazol-5-yl	Cl	Cl	444
65	cyanomethyl	Cl	Cl	416
66	cyanomethyl	F	CO ₂ Me	424
67	cyclopropyl	cyano	F	392
68	2,2,2-trifluoroethyl	(dimethylamino)carbonyl	F	480
69	pyrimidin-5-yl	(methoxycarbonyl)amino	F	478
70	pyrimidin-5-yl	[(methylamino)carbonyl] amino	F	477
71	trifluoromethyl	(methylamino)carbonyl	F	452
72	trifluoromethyl	(methylamino)carbonyl	Cl	468

The following compounds in Table 5 were prepared by methods analogous to those described in Example 2.

Table 5

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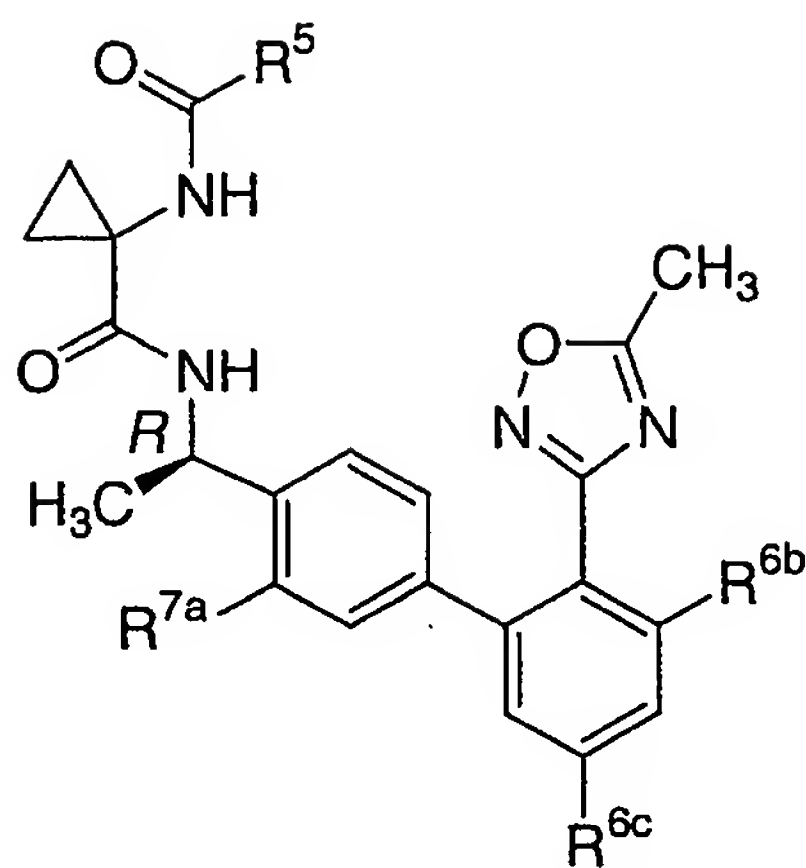


Example	R ⁵	R ^{6a}	ES MS, M+H ⁺
73	2,2,2-trifluoroethyl	(methylamino)carbonyl	466
74	isoxazol-5-yl	(methoxyamino)carbonyl	467
75	2,2,2-trifluoroethyl	(cyclopropylamino)carbonyl	492
76	2,2,2-trifluoroethyl	(cyclobutylamino)carbonyl	506

The following compounds in Table 6 were prepared by methods analogous to those described in Example 1.

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Table 6

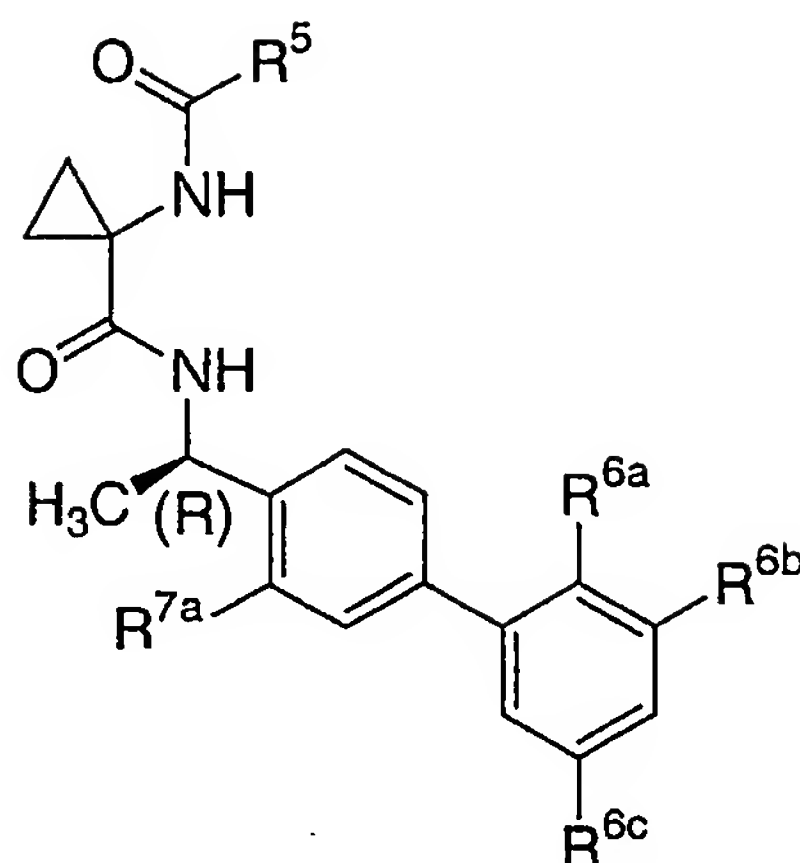


Example	R ⁵	R ^{6b}	R ^{6c}	R ^{7a}	ES MS, M+H ⁺
77	2,2,2-trifluoroethyl	F	H	H	491
78	isoxazol-5-yl	F	H	H	476
79	pyrimidin-5-yl	H	H	F	487
80	trifluoromethyl	H	H	F	477
81	pyrimidin-5-yl	H	Cl	F	521
82	trifluoromethyl	H	Cl	F	511
83	pyrimidin-5-yl	H	methyl	F	501
84	trifluoromethyl	H	methyl	F	491
85	pyrimidin-5-yl	H	F	F	505
86	trifluoromethyl	H	F	F	495

5

The following compounds in Table 7 were prepared by methods analogous to those described in Example 1.

Table 7



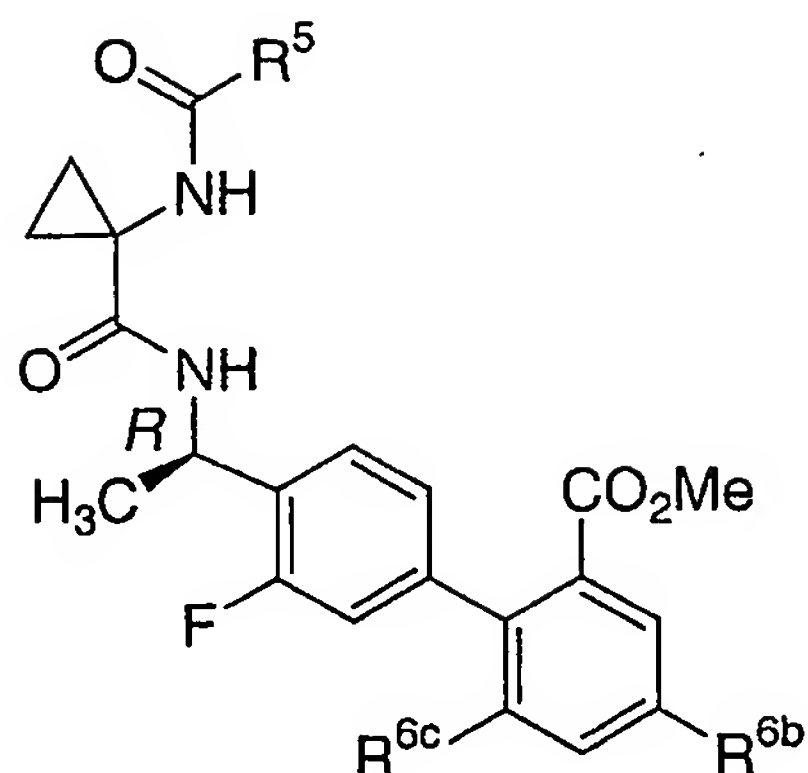
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Ex.	R ⁵	R ^{6a}	R ^{6b}	R ^{6c}	R ^{7a}	ES MS, M+H ⁺
87	pyrimidin-5-yl	methoxy	F	F	H	453
88	trifluoromethyl	methoxy	F	F	H	443
89	pyrimidin-5-yl	2-methyl-2H-tetrazol-5-yl	H	F	F	505
90	trifluoromethyl	2-methyl-2H-tetrazol-5-yl	H	F	F	495
91	trifluoromethyl	CO ₂ Me	H	Cl	F	487
92	chlorodifluoromethyl	CO ₂ Me	H	Cl	F	503
93	trifluoromethyl	CO ₂ Me	H	methyl	F	467
94	chlorodifluoromethyl	CO ₂ Me	H	methyl	F	483
95	trifluoromethyl	3-methyl-1,2,4-oxadiazol-5-yl	H	F	F	495
96	trifluoromethyl	3-methyl-1,2,4-oxadiazol-5-yl	H	Cl	F	511
97	chlorodifluoromethyl	3-methyl-1,2,4-oxadiazol-5-yl	H	Cl	F	527
98	trifluoromethyl	3-methyl-1,2,4-oxadiazol-5-yl	H	methyl	F	491
99	chlorodifluoromethyl	3-methyl-1,2,4-oxadiazol-5-yl	H	methyl	F	507

Ex.	R5	R6a	R6b	R6c	R7a	ES MS, M+H ⁺
		5-yl				
100	trifluoromethyl	CO ₂ Me	H	F	F	471
101	chlorodifluoromethyl	CO ₂ Me	H	F	F	487
102	pyrimidin-5-yl	2-methyl-2H-tetrazol-5-yl	H	Cl	F	521
103	trifluoromethyl	2-methyl-2H-tetrazol-5-yl	H	Cl	F	511
104	pyrimidin-5-yl	2-methyl-2H-tetrazol-5-yl	H	methyl	F	501
105	trifluoromethyl	2-methyl-2H-tetrazol-5-yl	H	methyl	F	491
106	trifluoromethyl	(methylamino)carbonyl	Cl	H	F	486
107	trifluoromethyl	(methoxycarbonyl)amino	Cl	H	F	502
108	trifluoromethyl	(isopropoxycarbonyl)- amino	Cl	H	F	530
109	pyrimidin-5-yl	(isopropoxy- carbonyl)amino	Cl	H	F	540
110	trifluoromethyl	(methoxycarbonyl)amino	F	H	F	486
111	trifluoromethyl	2-methoxy-2-oxoethyl	F	H	F	485
112	trifluoromethyl	(methylamino)carbonyl	F	H	F	470
113	trifluoromethyl	methoxymethyl	Cl	H	F	473
114	trifluoromethyl	hydroxy	Cl	Cl	H	479
115	pyrimidin-5-yl	(methoxycarbonyl)amino	F	H	F	496
116	pyrimidin-5-yl	(methoxycarbonyl)amino	Cl	H	F	512

The following compounds in Table 8 were prepared by methods analogous to those described in Example 1.

Table 8



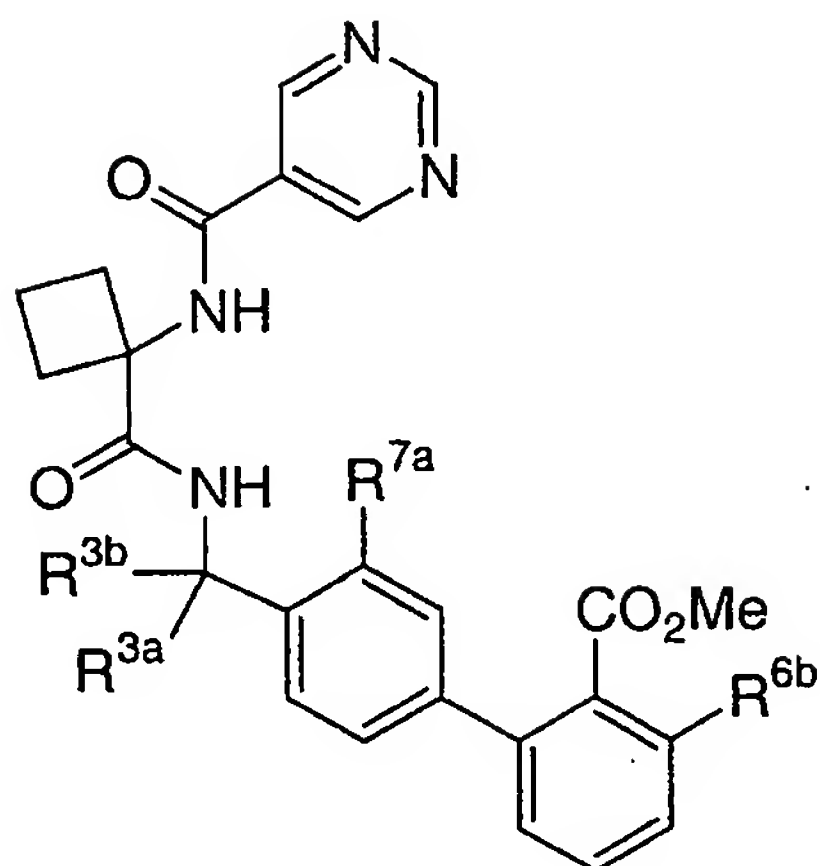
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Example	R ⁵	R ^{6b}	R ^{6c}	ES MS, M+H ⁺
117	trifluoromethyl	H	methyl	467
118	chloro(difluoro)methyl	H	methyl	483
119	trifluoromethyl	Cl	H	487
120	trifluoromethyl	methyl	H	467
121	chloro(difluoro)methyl	methyl	H	483

The following compounds in Table 9 were prepared by methods analogous to those described in Example 3, using the commercially available 1-[(tert-butoxycarbonyl)amino]cyclobutanecarboxylic acid instead of 1-[(tert-butoxycarbonyl)amino]cyclopropanecarboxylic acid.

10

Table 9



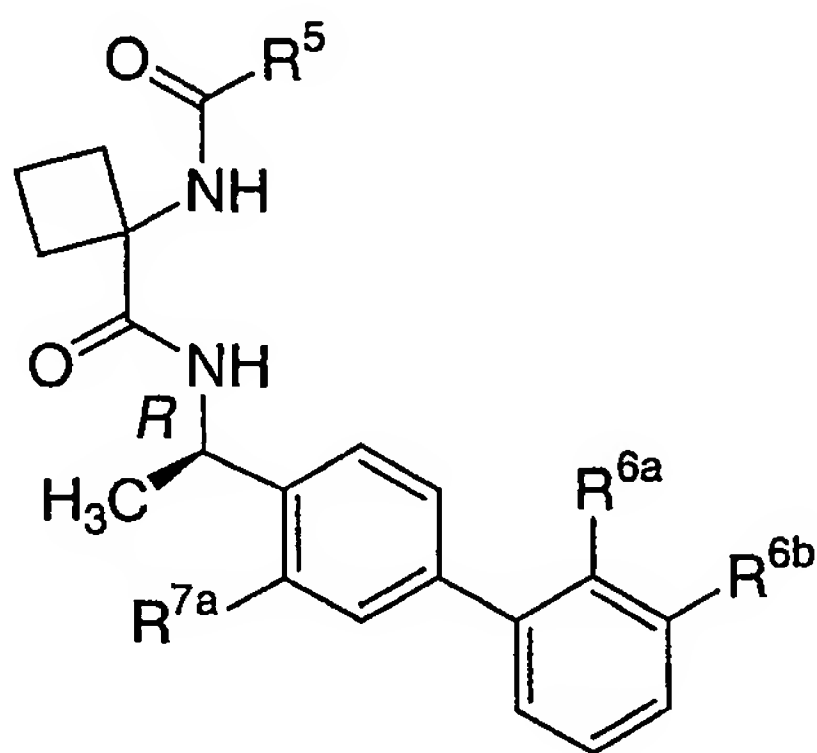
Example	R ^{3a} , R ^{3b}	R ^{6b}	R ^{7a}	ES MS, M+H ⁺
122	Me, Me	F	H	491

5

The following compounds in Table 10 were prepared by methods analogous to those described in Example 1, using the commercially available 1-[(tert-butoxycarbonyl)amino]cyclobutanecarboxylic acid instead of 1-[(tert-butoxycarbonyl)amino]cyclopropanecarboxylic acid.

10

Table 10

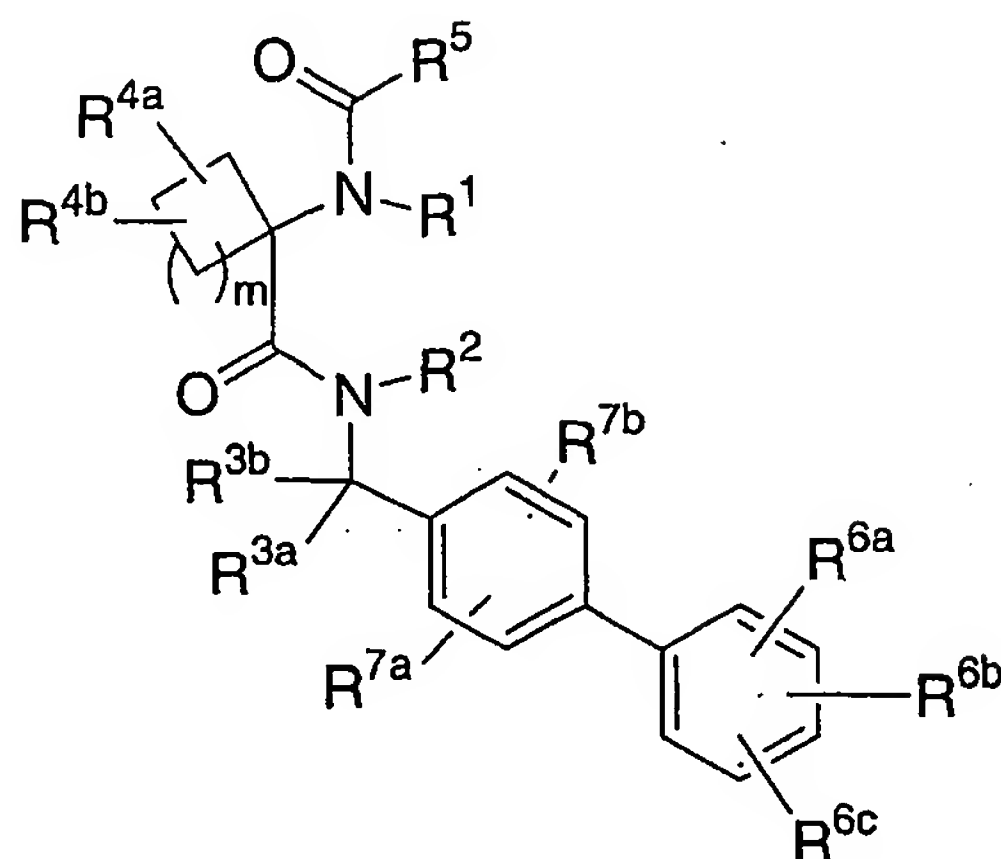


Example	R5	R6a	R6b	R7a	ES MS, M+H ⁺
123	trifluoromethyl	3-methyl-1,2,4-oxadiazol-5-yl	F	F	509
124	chlorodifluoromethyl	3-methyl-1,2,4-oxadiazol-5-yl	F	F	525
125	pyrimidin-5-yl	3-methyl-1,2,4-oxadiazol-5-yl	F	F	519
126	trifluoromethyl	CO ₂ Me	F	F	485
127	chlorodifluoromethyl	CO ₂ Me	F	F	501
128	pyrimidin-5-yl	CO ₂ Me	F	F	495
129	pyrimidin-5-yl	CO ₂ Me	F	H	477
130	pyrimidin-5-yl	2-methyl-2H-tetrazol-5-yl	F	F	519
131	trifluoromethyl	CO ₂ Me	Cl	F	501
132	chlorodifluoromethyl	CO ₂ Me	Cl	F	517
133	difluoromethyl	CO ₂ Me	Cl	F	483

WHAT IS CLAIMED IS:

1. A compound of formula I and pharmaceutically acceptable salts thereof:

5



I

wherein

R¹ and R² are independently selected from

- 10 (1) hydrogen and
(2) C₁₋₄ alkyl;

R^{3a} is selected from

- (1) hydrogen and
(2) C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms;

15 R^{3b} is C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms;

R^{4a} and R^{4b} are independently selected from

- (1) hydrogen,
(2) halogen, and
(3) C₁₋₄ alkyl optionally substituted with 1 to 4 groups selected

20 from halogen, OR^a, OC(O)R^a, S(O)_kR^d, OS(O)₂R^d, and NR¹R², or

R^{4a} and R^{4b} together with the carbon atom to which they are both attached form an exo-cyclic methylene optionally substituted with 1 to 2 groups selected from C₁₋₄ alkyl optionally substituted with 1-5 halogens and C₁₋₄ alkyloxy;

R⁵ is selected from

- 25 (1) C₁₋₆ alkyl optionally substituted with 1 to 5 groups
independently selected from halogen, nitro, cyano, OR^a, SR^a, COR^a, SO₂R^d,

CO₂R^a, OC(O)R^a, NR^bR^c, NR^bC(O)R^a, NR^bC(O)₂R^a, C(O)NR^bR^c, C₃₋₈ cycloalkyl,

(2) C₃₋₈ cycloalkyl optionally substituted with 1 to 5 groups independently selected from halogen, nitro, cyano and phenyl,

5 (3) C₃₋₆ alkynyl,

(4) C₂₋₆ alkenyl optionally substituted with hydroxyethyl,

(5) (CH₂)_k-aryl optionally substituted with 1 to 3 groups independently selected from halogen, nitro, cyano, OR^a, SR^a, C(O)₂R^a, C₁₋₄ alkyl and C₁₋₃ haloalkyl, wherein aryl is selected from phenyl, 3,4-methylenedioxyphenyl and naphthyl;

10 (6) (CH₂)_k-heterocycle optionally substituted with 1 to 3 groups independently selected from halogen, nitro, cyano, OR^a, SR^a, C₁₋₄ alkyl and C₁₋₃ haloalkyl wherein said heterocycle is selected from (a) a 5-membered heteroaromatic ring having a ring heteroatom selected from N, O and S, and optionally having up to 3
15 additional ring nitrogen atoms wherein said ring is optionally benzo-fused; (b) a 6-membered heteroaromatic ring containing from 1 to 3 ring nitrogen atoms and N-oxides thereof, wherein said ring is optionally benzo-fused; and (c) a 5- or 6-membered non-aromatic heterocyclic ring selected from tetrahydrofuranyl, 5-oxo-tetrahydrofuranyl, 2-oxo-2H-pyranal, 6-oxo-1,6-dihydropyridazinyl,

20 (7) C(O)₂R^a, and

(8) C(O)NR^bR^c;

R^{6a} is selected from

(1) C₁₋₈ alkyl optionally substituted with 1-5 groups independently selected from halogen, nitro, cyano, COR^a, CO₂R^a, C(O)NR^bR^c, OR^a, OC(O)R^a,
25 SR^a, SO₂R^d, S(O)R^d, NR^bR^c, NR^bC(O)R^a, NR^bSO₂R^d, NR^bCO₂R^a,

(2) C₃₋₈ cycloalkyl,

(3) C₂₋₈ alkenyl optionally substituted with CO₂R^a,

(4) halogen,

(5) cyano,

30 (6) nitro,

(7) NR^bR^c,

(8) NR^bC(O)R^a,

(9) NR^bCO₂R^a,

(10) NR^bC(O)NR^bR^c,

- (11) $\text{NR}^b\text{C}(\text{O})\text{NR}^b\text{CO}_2\text{R}^a$,
 (12) $\text{NR}^b\text{SO}_2\text{R}^d$,
 (13) CO_2R^a ,
 (14) COR^a ,
 5 (15) $\text{C}(\text{O})\text{NR}^b\text{R}^c$,
 (16) $\text{C}(\text{O})\text{NHO}\text{R}^a$,
 (17) $\text{C}(=\text{NOR}^a)\text{R}^a$,
 (18) $\text{C}(=\text{NOR}^a)\text{NR}^b\text{R}^c$,
 (19) OR^a ,
 10 (20) $\text{OC}(\text{O})\text{R}^a$,
 (21) $\text{S}(\text{O})_k\text{R}^d$,
 (22) $\text{SO}_2\text{NR}^b\text{R}^c$, and
 (23) optionally substituted heterocycle where the heterocycle is a 5-membered heteroaromatic ring having a ring heteroatom selected from N, O and S, and optionally having up to 3 additional ring nitrogen atoms, 4,5-dihydro-oxazolyl and 4,5-dihydro-1,2,4-oxadiazolyl, and wherein said substituent is 1 to 3 groups independently selected from C_{1-4} alkyl optionally substituted with 1 to 5 halogen atoms, OR^a or $\text{OC}(\text{O})\text{R}^a$,
 15 R^{6b} and R^{6c} are independently selected from
 20 (1) hydrogen, and
 (2) a group from R^{6a} ; with the proviso that not more than one of R^{6a} , R^{6b} , and R^{6c} is a heterocycle;
 R^{7a} and R^{7b} are independently selected from
 25 (1) hydrogen,
 (2) halogen,
 (3) cyano,
 (4) nitro,
 (5) OR^a ,
 (6) CO_2R^a ,
 30 (7) $\text{C}(\text{O})\text{NR}^b\text{R}^c$,
 (8) C_{1-4} alkyl optionally substituted with 1 to 5 halogen atoms,
 (9) NR^bR^c , and
 (10) $\text{S}(\text{O})_k\text{R}^d$;

R^a is selected from

- (1) hydrogen,
 (2) C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms,
 (3) phenyl optionally substituted with 1 to 3 groups independently
 selected from halogen, cyano, nitro, OH, C₁₋₄ alkyloxy, C₃₋₆ cycloalkyl and C₁₋₄
 5 alkyl optionally substituted with 1 to 5 halogen atoms,
 (4) C₃₋₆ cycloalkyl, and
 (5) pyridyl optionally substituted with 1 to 3 groups independently
 selected from halogen and C₁₋₄ alkyl;

R^b and R^c are independently selected from

- 10 (1) hydrogen,
 (2) C₁₋₄ alkyl optionally substituted with 1 to 5 groups
 independently selected from halogen, amino, mono-C₁₋₄alkylamino, di-
 C₁₋₄alkylamino, and SO₂R^d,
 (3) (CH₂)_k-phenyl optionally substituted with 1 to 3 groups
 15 selected from halogen, cyano, nitro, OH, C₁₋₄ alkyloxy, C₃₋₆ cycloalkyl and C₁₋₄
 alkyl optionally substituted with 1 to 5 halogen atoms, and
 (4) C₃₋₆ cycloalkyl, or

R^b and R^c together with the nitrogen atom to which they are attached form a 4-, 5-, or
 6-membered ring optionally containing an additional heteroatom selected from N, O,
 20 and S; or

R^b and R^c together with the nitrogen atom to which they are attached form a cyclic
 imide;

R^d is selected from

- (1) C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms,
 25 (2) C₁₋₄ alkyloxy, and
 (3) phenyl optionally substituted with 1 to 3 groups selected from
 halogen, cyano, nitro, OH, C₁₋₄ alkyloxy, C₃₋₆ cycloalkyl and C₁₋₄ alkyl optionally
 substituted with 1 to 5 halogen atoms;

k is 0, 1 or 2; and

30 m is 0 or 1.

2. A compound of Claim 1 wherein R¹ and R² are each hydrogen.
3. A compound of Claim 1 wherein wherein R^{3a} is hydrogen and
 35 R^{3b} is C₁₋₄ alkyl.

4. A compound of Claim 1 wherein one of R^{4a} and R^{4b} is hydrogen and the other is selected from hydrogen, halogen and C₁₋₄ alkyl optionally substituted with a group selected from halogen, OR^a, OC(O)R^a, S(O)_kR^d, OS(O)₂R^d and NR¹R², or R^{4a} and R^{4b} together with the carbon atom to which they are both attached form an exo-cyclic methylene.
5. A compound of Claim 1 wherein R^{4a} and R^{4b} are each hydrogen.
6. A compound of Claim 1 wherein R⁵ is C₁₋₆ alkyl optionally substituted with 1 to 5 groups independently selected from halogen, nitro, cyano, OR^a, SR^a, COR^a, SO₂R^d, CO₂R^a, OC(O)R^a, NR^bR^c, NR^bC(O)R^a, C(O)NR^bR^c, and C₃₋₈ cycloalkyl.
7. A compound of Claim 1 wherein R⁵ is selected from C₁₋₅ alkyl and C₁₋₃ alkyl substituted with 1 to 3 groups selected from halogen, cyano, hydroxy, C₁₋₄ alkoxy and C₁₋₄ alkoxy carbonyl.
8. A compound of Claim 1 wherein R⁵ is selected from C₁₋₃ alkyl substituted with 1 to 5 halogen atoms, or a group selected from cyano, hydroxy, C₁₋₄ alkoxy and C₁₋₄ alkoxy carbonyl.
9. A compound of Claim 1 wherein R⁵ is C₃₋₆ cycloalkyl optionally substituted with 1 to 3 groups independently selected from halogen, nitro, cyano and phenyl.
10. A compound of Claim 1 wherein R⁵ is (CH₂)_k-aryl optionally substituted with 1 to 3 groups independently selected from halogen, nitro, cyano, OR^a, SR^a, C₁₋₄ alkyl and C₁₋₃ haloalkyl, wherein aryl is selected from phenyl, 3,4-methylenedioxyphenyl and naphthyl.
11. A compound of Claim 1 wherein (CH₂)_k-heterocycle optionally substituted with 1 to 3 groups independently selected from halogen, nitro, cyano, OR^a, SR^a, C₁₋₄ alkyl and C₁₋₃ haloalkyl wherein said heterocycle is selected

from (a) a 5-membered heteroaromatic ring having a ring heteroatom selected from N, O and S, and optionally having up to 3 additional ring nitrogen atoms wherein said ring is optionally benzo-fused; and (b) a 6-membered heteroaromatic ring containing from 1 to 3 ring nitrogen atoms wherein said ring is optionally benzo-fused.

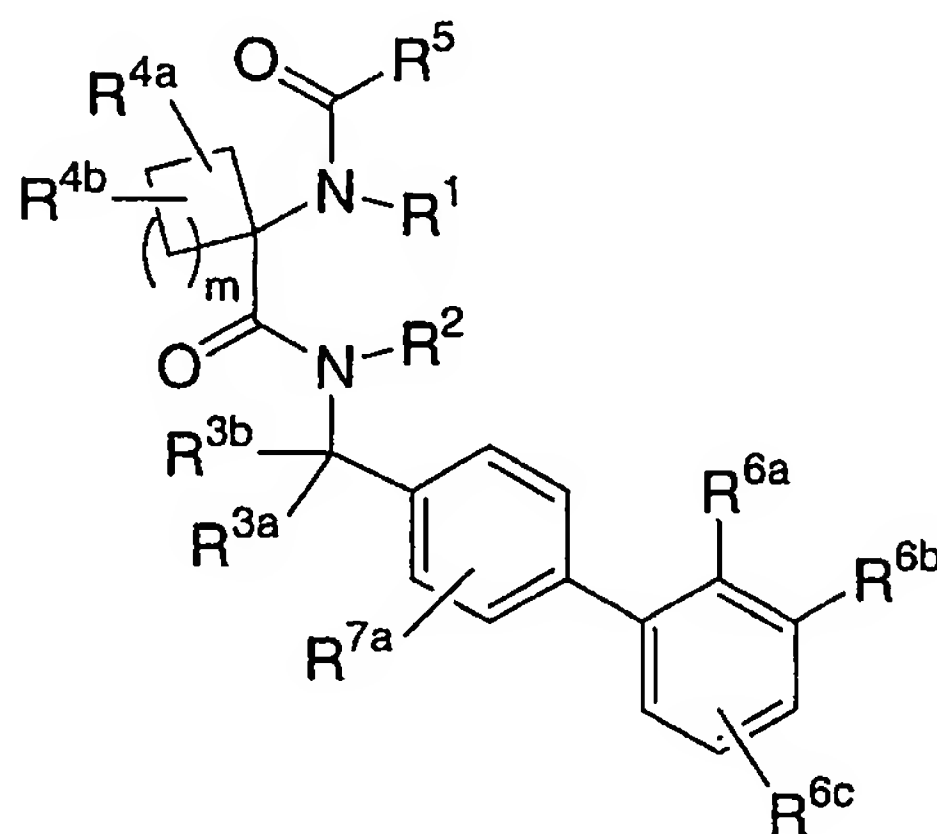
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12. A compound of Claim 1 wherein R⁵ is (CH₂)_k-heterocycle optionally substituted with 1 to 2 groups independently selected from halogen, nitro, cyano, OR^a, SR^a, C₁₋₄ alkyl and C₁₋₃ haloalkyl wherein said heterocycle is selected from isoxazolyl, thienyl, pyridinyl, benzothienyl, furyl, oxadiazolyl, 1-oxidopyridinyl, pyrazolyl, imidazolyl, 1,2,4-triazolyl, thiazolyl, 5-oxotetrahydrofuranyl, 2-oxo-2H-pyranyl, 6-oxo-1,6-dihydropyridazinyl, oxazolyl, pyridazinyl, pyrimidinyl and quinoxaliny.

13. A compound of Claim 1 wherein R⁵ is selected from 5-isoxazolyl, 5-pyrimidinyl, 5-bromo-3-pyridyl and N-oxide thereof, and 5-trifluoromethyl-3-pyridyl.

14. A compound of Claim 1 wherein R⁵ is selected from isoxazolyl optionally substituted with C₁₋₄ alkyl, pyrimidinyl, pyridinyl optionally substituted with C₁₋₄ alkyl and N-oxides thereof.

15. A compound of Claim 1 having the formula I(1):



I(1)

25

wherein m, R¹, R², R^{3a}, R^{3b}, R^{4a}, R^{4b}, R⁵, R^{6a}, R^{6b}, R^{6c} and R^{7a} are as defined in Claim 1.

16. A compound of Claim 15 wherein R^{6a} is selected from (1)
5 CO₂R^a, (2) C(O)NHO^a, (3) cyano, (4) halogen, (5) O^a, (6) C₁₋₈ alkyl optionally
substituted with 1-5 halogen atoms, or a group selected from CO₂R^a, C(O)NR^bR^c
and O^a, (7) C(O)NR^bR^c, (8) NR^bC(O)NR^bR^c, (9) NR^bC(O)O^a, and (10)
optionally substituted heterocycle where the heterocycle is selected from oxadiazolyl
and tetrazolyl and wherein said substituent is 1 to 3 groups independently selected
10 from C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms, O^a or OC(O)R^a.

17. A compound of Claim 15 wherein R^{6a} is selected from
CO₂R^a, C(O)NHO^a, methyltetrazolyl, methyloxadiazolyl, NR^bC(O)NR^bR^c, and
NR^bC(O)O^a.

15

18. A compound of Claim 15 wherein R^{6b} is selected from
hydrogen, halogen and CO₂R^a.

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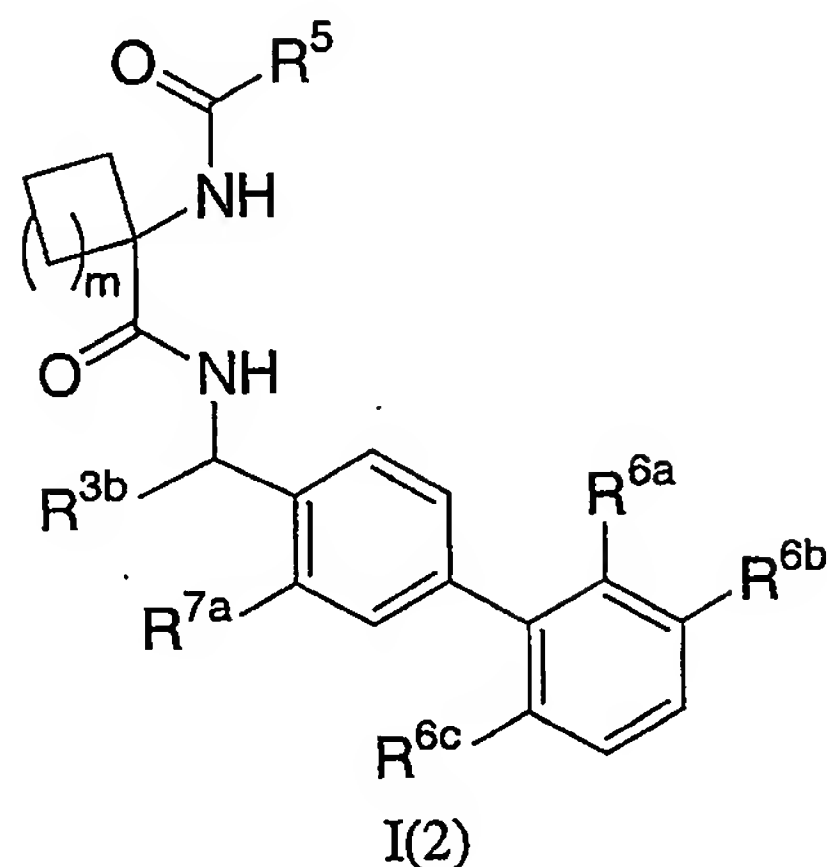
19. A compound of Claim 15 wherein R^{6b} is hydrogen or halogen.

20. A compound of Claim 15 wherein R^{6a} is selected from (1)
CO₂R^a, (2) C(O)NHO^a, (3) cyano, (4) halogen, (5) O^a, (6) C₁₋₈ alkyl optionally
substituted with 1-5 halogen atoms, or a group selected from CO₂R^a, C(O)NR^bR^c
and O^a, (7) C(O)NR^bR^c, (8) NR^bC(O)NR^bR^c, (9) NR^bC(O)O^a, and (10)
25 optionally substituted heterocycle where the heterocycle is selected from oxadiazolyl
and tetrazolyl and wherein said substituent is 1 to 3 groups independently selected
from C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms, O^a or OC(O)R^a;
R^{6b} is selected from hydrogen, fluorine and chlorine; and R^{6c} is hydrogen.

30

21. A compound of Claim 15 wherein R⁵ is selected from C₁₋₄
alkyl optionally substituted with 1 to 5 halogen atoms or a cyano group, C₃₋₆
cycloalkyl, isoxazolyl, pyrimidinyl and pyridinyl (and N-oxide thereof) optionally
substituted with halogen.

22. A compound of Claim 1 having the formula I(2):



5

wherein m, R^{3b}, R^{4a}, R^{4b}, R⁵, R^{6a}, R^{6b}, R^{6c} and R^{7a} are as defined in Claim 1.

23. A compound of Claim 22 wherein R^{3b} is methyl.

10

24. A compound of Claim 22 wherein R^{6b} is hydrogen or halogen.

25. A compound of Claim 22 wherein R^{6b} is hydrogen.

26. A compound of Claim 22 wherein R^{6b} is fluorine or chlorine.

15

27. A compound of Claim 22 wherein R^{6a} is selected from (1) CO₂R^a, (2) C(O)NHO^a, (3) cyano, (4) halogen, (5) OR^a, (6) C₁₋₈ alkyl optionally substituted with 1-5 halogen atoms, or a group selected from CO₂R^a, C(O)NR^bR^c and OR^a, (7) C(O)NR^bR^c, (8) NR^bC(O)NR^bR^c, (9) NR^bC(O)OR^a, and (10) optionally substituted heterocycle where the heterocycle is selected from oxadiazolyl and tetrazolyl and wherein said substituent is 1 to 3 groups independently selected from C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms, OR^a or OC(O)R^a.

20

28. A compound of Claim 22 wherein R^{6a} is selected from CO₂R^a, C(O)NHO^a, methyltetrazolyl, methyloxadiazolyl, NR^bC(O)NR^bR^c, and NR^bC(O)OR^a.

25

29. A compound of Claim 22 wherein R^{6a} is selected from CO₂R^a, methyltetrazolyl and methyloxadiazolyl.

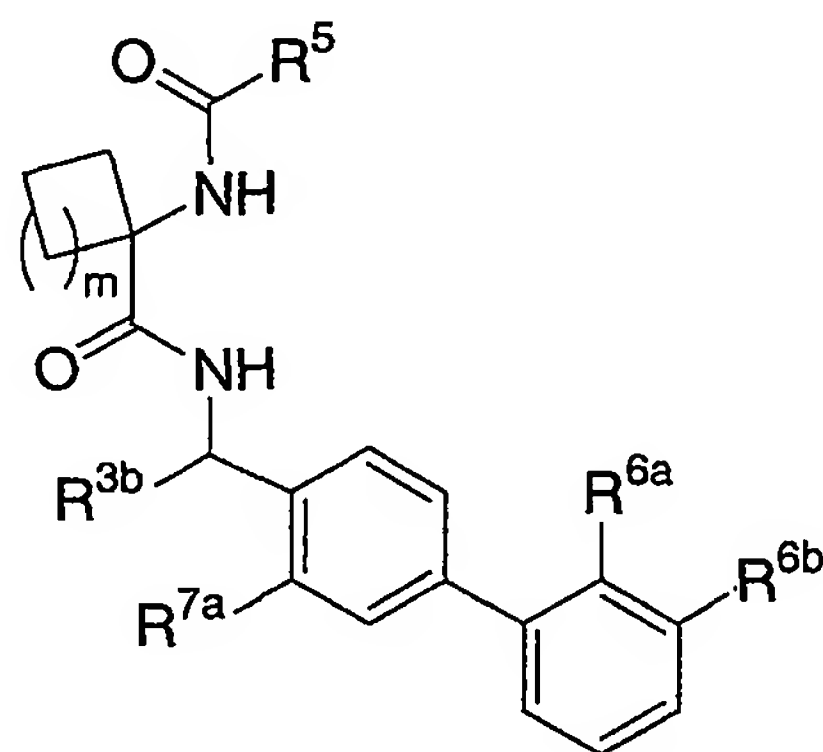
30. A compound of Claim 22 wherein R^{6c} is hydrogen.

31. A compound of Claim 22 wherein R^{7a} is hydrogen or halogen.

32. A compound of Claim 22 wherein R^{7a} is hydrogen or fluorine.

33. A compound of Claim 22 wherein R⁵ is selected from C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms or a cyano group, C₃₋₆ cycloalkyl, isoxazolyl, pyrimidinyl and pyridinyl (and N-oxide thereof) optionally substituted with halogen.

34. A compound of Claim 1 having the formula I(3):



I(3)

wherein m is 0 or 1, R^{6a} is 2-methyl-2H-tetrazol-5-yl, 3-methyl-1,2,4-oxadiazol-5-yl, CO₂R^a or C(O)NHO^a wherein R^a is C₁₋₄ alkyl; R^{6b} is hydrogen, fluorine or chlorine; R^{3b} is C₁₋₄ alkyl; R⁵ is selected from C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms or a cyano group, C₃₋₆ cycloalkyl, isoxazolyl, pyrimidinyl and pyridinyl (and N-oxide thereof) optionally substituted with halogen or trifluoromethyl, particularly trifluoromethyl, difluoromethyl, chlorodifluoromethyl; and R^{7a} is hydrogen or fluorine.

m	R5	R6a	R6b	R6c	R7a	*
0	pyrimidin-5-yl	CO ₂ CH ₃	F	H	F	S
0	CH ₃	CO ₂ CH ₃	F	H	F	R
0	5-Br-pyridin-3-yl	CO ₂ CH ₃	F	H	F	R
0	5-Br-1-oxido-pyridin-3-yl	CO ₂ CH ₃	F	H	F	R
0	CF ₃	CO ₂ CH ₃	H	H	F	R
0	pyrimidin-5-yl	CO ₂ CH ₃	H	H	F	R
0	CClF ₂	CO ₂ CH ₃	F	H	F	R
0	5-(CF ₃)pyridin-3-yl	CO ₂ CH ₃	F	H	F	R
0	CClF ₂	CO ₂ CH ₃	Cl	H	F	R
0	CHF ₂	CO ₂ CH ₃	F	H	F	R
0	CF ₂ CF ₃	CO ₂ CH ₃	F	H	F	R
0	CHF ₂	CO ₂ CH ₃	Cl	H	F	R
0	CH ₃	3-CH ₃ -1,2,4-oxadiazol-5-yl	F	H	H	R
0	CH ₂ CN	3-CH ₃ -1,2,4-oxadiazol-5-yl	F	H	H	R
0	CH ₂ CF ₃	3-CH ₃ -1,2,4-oxadiazol-5-yl	F	H	H	R
0	isoxazol-5-yl	3-CH ₃ -1,2,4-oxadiazol-5-yl	F	H	H	R
0	CH ₂ CF ₃	3-CH ₃ -1,2,4-oxadiazol-5-yl	F	H	F	S
0	CH ₂ CF ₃	3-CH ₃ -1,2,4-oxadiazol-5-yl	F	H	F	R
0	CH ₂ CN	3-CH ₃ -1,2,4-oxadiazol-5-yl	F	H	F	(±)
0	CH ₂ CF ₃	3-CH ₃ -1,2,4-oxadiazol-5-yl	F	H	F	(±)
0	pyrimidin-5-yl	3-CH ₃ -1,2,4-oxadiazol-5-yl	F	H	F	(±)
0	CClF ₂	3-CH ₃ -1,2,4-oxadiazol-5-yl	F	H	F	R
0	pyrimidin-5-yl	3-CH ₃ -1,2,4-oxadiazol-5-yl	F	H	F	R
0	CHF ₂	3-CH ₃ -1,2,4-oxadiazol-5-yl	F	H	F	R
0	CH ₂ CN	2-CH ₃ -tetrazol-5-yl	F	H	H	R
0	CH ₂ CF ₃	2-CH ₃ -tetrazol-5-yl	F	H	H	R
0	CH ₂ CN	1-CH ₃ -tetrazol-5-yl	F	H	H	R
0	CH ₂ CF ₃	1-CH ₃ -tetrazol-5-yl	F	H	H	R
0	CH ₃	1-CH ₃ -tetrazol-5-yl	F	H	H	R

m	R5	R6a	R6b	R6c	R7a	*
0	isoxazol-5-yl	2-CH ₃ -tetrazol-5-yl	F	H	F	(±)
0	CH ₂ CF ₃	2-CH ₃ -tetrazol-5-yl	F	H	F	(±)
0	pyrimidin-5-yl	2-CH ₃ -tetrazol-5-yl	F	H	F	(±)
0	CF ₃	2-CH ₃ -tetrazol-5-yl	F	H	F	S
0	CClF ₂	2-CH ₃ -tetrazol-5-yl	F	H	F	R
0	CHF ₂	2-CH ₃ -tetrazol-5-yl	F	H	F	R
0	CH ₂ CF ₃	cyano	F	H	H	R
0	CH ₂ CF ₃	difluoromethoxy	H	H	H	R
0	CH ₂ CF ₃	trifluoromethoxy	H	H	H	R
0	CH ₂ CF ₃	trifluoromethyl	F	H	H	R
0	CH ₂ CF ₃	Cl	Cl	H	H	R
0	isoxazol-5-yl	trifluoromethyl	F	H	H	R
0	CH ₂ CN	trifluoromethyl	F	H	H	R
0	isoxazol-5-yl	Cl	Cl	H	H	R
0	CH ₂ CN	Cl	Cl	H	H	R
0	CH ₂ CN	F	CO ₂ Me	H	H	R
0	cyclopropyl	cyano	F	H	H	R
0	CH ₂ CF ₃	CON(CH ₃) ₂	F	H	H	R
0	pyrimidin-5-yl	NHCO ₂ CH ₃	F	H	H	R
0	pyrimidin-5-yl	NHCONHCH ₃	F	H	H	R
0	CF ₃	CONHCH ₃	F	H	H	R
0	CF ₃	CONHCH ₃	Cl	H	H	R
0	CH ₂ CF ₃	CONHCH ₃	F	H	H	R
0	isoxazol-5-yl	CONHOCH ₃	F	H	H	R
0	CH ₂ CF ₃	CONH-cyclopropyl	F	H	H	R
0	CH ₂ CF ₃	CONH-cyclobutyl	F	H	H	R
0	CH ₂ CF ₃	5-CH ₃ -1,2,4-oxadiazol-3-yl	F	H	H	R
0	isoxazol-5-yl	5-CH ₃ -1,2,4-oxadiazol-3-yl	F	H	H	R
0	pyrimidin-5-yl	5-CH ₃ -1,2,4-oxadiazol-3-yl	H	H	F	R
0	CF ₃	5-CH ₃ -1,2,4-oxadiazol-3-yl	H	H	F	R
0	pyrimidin-5-yl	5-CH ₃ -1,2,4-oxadiazol-3-yl	H	5-Cl	F	R
0	CF ₃	5-CH ₃ -1,2,4-oxadiazol-3-yl	H	5-Cl	F	R

m	R5	R6a	R6b	R6c	R7a	*
0	pyrimidin-5-yl	5-CH ₃ -1,2,4-oxadiazol-3-yl	H	5-CH ₃	F	R
0	CF ₃	5-CH ₃ -1,2,4-oxadiazol-3-yl	H	5-CH ₃	F	R
0	pyrimidin-5-yl	5-CH ₃ -1,2,4-oxadiazol-3-yl	H	5-F	F	R
0	CF ₃	5-CH ₃ -1,2,4-oxadiazol-3-yl	H	5-F	F	R
0	pyrimidin-5-yl	methoxy	F	5-F	H	R
0	CF ₃	methoxy	F	5-F	H	R
0	pyrimidin-5-yl	2-CH ₃ -2H-tetrazol-5-yl	H	5-F	F	R
0	CF ₃	2-CH ₃ -2H-tetrazol-5-yl	H	5-F	F	R
0	CF ₃	CO ₂ CH ₃	H	5-Cl	F	R
0	CClF ₂	CO ₂ CH ₃	H	5-Cl	F	R
0	CF ₃	CO ₂ CH ₃	H	5-CH ₃	F	R
0	CClF ₂	CO ₂ CH ₃	H	5-CH ₃	F	R
0	CF ₃	3-CH ₃ -1,2,4-oxadiazol-5-yl	H	5-F	F	R
0	CF ₃	3-CH ₃ -1,2,4-oxadiazol-5-yl	H	5-Cl	F	R
0	CClF ₂	3-CH ₃ -1,2,4-oxadiazol-5-yl	H	5-Cl	F	R
0	CF ₃	3-CH ₃ -1,2,4-oxadiazol-5-yl	H	5-CH ₃	F	R
0	CClF ₂	3-CH ₃ -1,2,4-oxadiazol-5-yl	H	5-CH ₃	F	R
0	CF ₃	CO ₂ CH ₃	H	5-F	F	R
0	CClF ₂	CO ₂ CH ₃	H	5-F	F	R
0	pyrimidin-5-yl	2-CH ₃ -2H-tetrazol-5-yl	H	5-Cl	F	R
0	CF ₃	2-CH ₃ -2H-tetrazol-5-yl	H	5-Cl	F	R
0	pyrimidin-5-yl	2-CH ₃ -2H-tetrazol-5-yl	H	5-CH ₃	F	R
0	CF ₃	2-CH ₃ -2H-tetrazol-5-yl	H	5-CH ₃	F	R
0	CF ₃	CONHCH ₃	Cl	H	F	R
0	CF ₃	NHCO ₂ CH ₃	Cl	H	F	R
0	CF ₃	NHCO ₂ CH(CH ₃) ₂	Cl	H	F	R
0	pyrimidin-5-yl	NHCO ₂ CH(CH ₃) ₂	Cl	H	F	R
0	CF ₃	NHCO ₂ CH ₃	F	H	F	R
0	CF ₃	2-methoxy-2-oxoethyl	F	H	F	R
0	CF ₃	CONHCH ₃	F	H	F	R
0	CF ₃	CH ₂ OCH ₃	Cl	H	F	R
0	CF ₃	hydroxy	Cl	5-Cl	H	R

m	R5	R6a	R6b	R6c	R7a	*
0	pyrimidin-5-yl	NHCO ₂ CH ₃	F	H	F	R
0	pyrimidin-5-yl	NHCO ₂ CH ₃	Cl	H	F	R
0	CF ₃	CO ₂ CH ₃	H	6-CH ₃	F	R
0	CClF ₂	CO ₂ CH ₃	H	6-CH ₃	F	R
0	CF ₃	CO ₂ CH ₃	Cl	H	F	R
0	CF ₃	CO ₂ CH ₃	CH ₃	H	F	R
0	CClF ₂	CO ₂ CH ₃	CH ₃	H	F	R
1	pyrimidin-5-yl	CO ₂ CH ₃	F	H	H	§
1	CF ₃	3-CH ₃ -1,2,4-oxadiazol-5-yl	F	H	F	R
1	CClF ₂	3-CH ₃ -1,2,4-oxadiazol-5-yl	F	H	F	R
1	pyrimidin-5-yl	3-CH ₃ -1,2,4-oxadiazol-5-yl	F	H	F	R
1	CF ₃	CO ₂ CH ₃	F	H	F	R
1	CClF ₂	CO ₂ CH ₃	F	H	F	R
1	pyrimidin-5-yl	CO ₂ CH ₃	F	H	F	R
1	pyrimidin-5-yl	CO ₂ CH ₃	F	H	H	R
1	pyrimidin-5-yl	2-CH ₃ -2H-tetrazol-5-yl	F	H	F	R
1	CF ₃	CO ₂ CH ₃	Cl	H	F	R
1	CClF ₂	CO ₂ CH ₃	Cl	H	F	R
1	CHF ₂	CO ₂ CH ₃	Cl	H	F	R

* stereoconfiguration at the indicated carbon,

§ R^{3a} is CH₃;

or a pharmaceutically acceptable salt thereof.

- 5 36. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 and pharmaceutically acceptable excipients.
- 10 37. A method of treatment or prevention of pain and inflammation comprising a step of administering, to a subject in need of such treatment or prevention, an effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof.

38. A method of treatment of osteoarthritis, repetitive motion pain, dental pain, cancer pain, myofascial pain, muscular injury pain, fibromyalgia pain, perioperative pain comprising a step of administering, to a subject in need of such treatment, an effective amount of a compound according to Claim 1 or a
5 pharmaceutically acceptable salt thereof.

39. A method of treatment or prevention of inflammatory pain caused by chronic obstructive pulmonary disease, asthma, inflammatory bowel disease, rhinitis, pancreatitis, cystitis (interstitial cystitis), uveitis, inflammatory skin
10 disorders, rheumatoid arthritis, edema resulting from trauma associated with burns, sprains or fracture, postsurgical intervention, osteoarthritis, rheumatic disease, teno-synovitis, or gout comprising a step of administering, to a subject in need of such treatment or prevention, an effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof.

15 40. A method of treatment or prevention of pain associated with angina, menstruation or cancer comprising a step of administering, to a subject in need of such treatment or prevention, an effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof.

20 41. A method of treatment of diabetic vasculopathy, post capillary resistance, diabetic symptoms associated with insulinitis, psoriasis, eczema, spasms of the gastrointestinal tract or uterus, Crohn's disease, ulcerative colitis, or pancreatitis comprising a step of administering, to a subject in need of such treatment, an effective
25 amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof.

42. A method of treatment or prevention of pain caused by pneumoconiosis, including aluminosis, anthracosis, asbestosis, chalicosis, ptilosis,
30 siderosis, silicosis, tabacosis, byssinosis, adult respiratory distress syndrome, bronchitis, allergic rhinitis, vasomotor rhinitis, liver disease, multiple sclerosis, atherosclerosis, Alzheimer's disease, septic shock, cerebral edema, headache, migraine, closed head trauma, irritable bowel syndrome, or nephritis comprising a step of administering, to a subject in need of such treatment or prevention of pain, an

effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Internatl Application No

PCT/US 03/03338

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C237/24 C07D213/82 C07D239/28 C07D271/06 C07D257/04
 C07D261/18 C07D413/12 //(C07D413/12,271:00,261:00),
 (C07D413/12,271:00,239:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 475 898 A (CIBA GEIGY AG) 18 March 1992 (1992-03-18) page 4, line 50 - line 52; claims 12,13 & CA 2 050 769 A 11 March 1992 (1992-03-11) cited in the application ---	1,36
A	WO 97 25315 A (SANOFI SA ;FERRARI BERNARD (FR); GOUGAT JEAN (FR); MUNEUX CLAUDE) 17 July 1997 (1997-07-17) abstract; claim 1 ---	1,36
A	WO 02 02513 A (BARBER CHRISTOPHER GORDON ;COOK ANDREW SIMON (GB); PRYDE DAVID CAM) 10 January 2002 (2002-01-10) page 11, paragraph 3; claim 1 ---	1,36
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

20 May 2003

Date of mailing of the international search report

18/06/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Rufet, J

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/US 03/03338

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 208 236 A (NEUSTADT BERNARD R) 4 May 1993 (1993-05-04) page 2, column 1, line 30 - line 44; claims 1,10 ---	1, 36
A	TATEAKI WAKAMIYA ET AL.: "Synthesis and stereochemistry of carnosadine,..." TETRAHEDRON LETTERS., vol. 27, no. 19, 1986, pages 2143-2144, XP002241722 OXFORD GB page 2144 ----	1
A	YEHIEL GAONI: "Stable monosubstituted triazenes by reduction of some tertiary azides" JOURNAL OF ORGANIC CHEMISTRY., vol. 59, no. 22, 1994, pages 6853-6855, XP002241723 EASTON US page 6853, column 2 -----	1

INTERNATIONAL SEARCH REPORT

Inter-
nal application No.
PCT/US 03/03338

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 37-42 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No

PCT/US 03/03338

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0475898	A	18-03-1992	AU 8375591 A	12-03-1992
			CA 2050769 A1	11-03-1992
			EP 0475898 A1	18-03-1992
			FI 914228 A	11-03-1992
			HU 59129 A2	28-04-1992
			IE 913165 A1	11-03-1992
			JP 4342571 A	30-11-1992
			NO 913542 A	11-03-1992
			PT 98903 A	31-07-1992
			ZA 9107143 A	29-04-1992
WO 9725315	A	17-07-1997	FR 2743562 A1	18-07-1997
			AT 203745 T	15-08-2001
			AU 1383297 A	01-08-1997
			BR 9707120 A	20-07-1999
			CA 2241788 A1	17-07-1997
			DE 69705930 D1	06-09-2001
			DE 69705930 T2	11-04-2002
			EP 0877737 A1	18-11-1998
			ES 2162231 T3	16-12-2001
			WO 9725315 A1	17-07-1997
			JP 2000504315 T	11-04-2000
			NO 983190 A	10-07-1998
			US 6015812 A	18-01-2000
			US 2003073641 A1	17-04-2003
			US 6100278 A	08-08-2000
			US 6313120 B1	06-11-2001
			US 6433185 B1	13-08-2002
			US 2002115685 A1	22-08-2002
WO 0202513	A	10-01-2002	AU 6777001 A	14-01-2002
			AU 6935301 A	21-01-2002
			EP 1296938 A1	02-04-2003
			EP 1296687 A2	02-04-2003
			WO 0203995 A2	17-01-2002
			WO 0202513 A1	10-01-2002
			NO 20026262 A	27-12-2002
			US 2002052370 A1	02-05-2002
			US 2002028799 A1	07-03-2002
US 5208236	A	04-05-1993	AU 5128793 A	12-04-1994
			MX 9305784 A1	31-03-1994
			WO 9406756 A1	31-03-1994